THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1941

ORIGINAL ARTICLES.

THE DIAGNOSIS OF HEMOPHILIA.*

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Hemophilia is recognized by the triad: inheritance through the female, occurrence only in the male, and a prolonged clotting time. While the diagnosis of hemophilia is usually simple, a number of difficulties may be encountered. A history of bleeding in the family is not always obtainable either because of incomplete records or because the case may be sporadic. Furthermore, another hemorrhagic disease, commonly designated as pseudohemophilia, is also hereditary. Female bleeders are by definition not hemophiliacs, but it is more important to know whether women who suffer from an inherited hemorrhagic condition have the same coagulation defect as a true case of hemophilia. Diagnosis cannot be made solely on a prolonged clotting time, for in severe prothrombinopenia, fibrinogenopenia, heparinemia and extreme thrombocytopenia a retardation of coagulation likewise occurs.

For an indisputable diagnosis of hemophilia, it is essential to have laboratory methods which specifically test the underlying cause of the disease. Recently the writer[12c] has reviewed the evidence for the conclusion that the delayed coagulation in hemophilia is due to an abnormal resistance of the platelets, which brings about an inadequate liberation of thromboplastin. On this basis, a test was developed which is a modification of the determination of the clotting time of recalcified plasma. The original test was employed as early as 1910 by Addis.[1] A few years later Howell[8] developed

* Part of this work was presented before the Central Society for Clinical Research, November 4, 1938, Chicago.

it into the standard method, which was unfortunately called by the misleading name, "prothrombin time." Gram[5] introduced certain useful improvements such as control of temperature and speed of centrifuging. Bancroft and Stanley-Brown[2] working with Kugelmass and later with the writer[3] further simplified the test, and applied it clinically. They, as had former investigators,[1,6,8,9,11] found that the clotting time of recalcified plasma was prolonged in hemophilia; but a similar finding was often also observed in the plasma of jaundiced patients. Further work by the author led to the finding that in hemophilic plasma, the speed of centrifuging markedly influenced the subsequent coagulation time. From this has developed the following test.

The Test. By venipuncture 4.5 cc. of blood are drawn and mixed immediately with 0.5 cc. of 0.1 M sodium oxalate. The blood is divided into two equal portions. One-half is centrifuged for 5 minutes at a rate not over 1000 r.p.m., while the other half is subjected to a centrifugation of 3000 r.p.m. for 5 minutes in an Angle centrifuge. The clotting time of each specimen is tested as follows: In a small test tube, 0.1 cc. of plasma is mixed with 0.2 cc. of 0.0125 M calcium chloride. The tube is placed in a water bath kept at 37½° C., and tilted occasionally. The exact time required for the formation of a solid clot is recorded.

Solutions: Sodium oxalate 0.1 M.: 1.34 gm. of sodium oxalate is dissolved in 100 cc. of distilled water. Calcium chloride 0.0125 M.: 0.14 gm. of anhydrous calcium chloride and 0.42 gm. sodium chloride are dissolved in 100 cc. of distilled water.

Results. The results obtained with this method yield interesting information. The clotting time of recalcified plasma is much shorter than that of whole blood. The normal for the Lee White test is 5 to 8 minutes, but for recalcified plasma it is only approximately 2 minutes. Apparently in the process of decalcification and subsequent recalcification the stability of the platelets is sufficiently disturbed to bring about extensive destruction of these cells with the liberation of considerable thromboplastin. In undisturbed blood, the disintegration of platelets is very much slower and therefore the coagulation is prolonged. In hemophilic blood, due to the great stability of the platelets, few of these cells undergo lysis, and when the blood is centrifuged at high speed the intact platelets are thrown down leaving the plasma poor in both free and potentially free thromboplastin. With slow centrifugation, however, the platelets remain suspended, and many suffer disintegration subsequent to recalcification. The marked influence that centrifuging has on the coagulation time of hemophilic plasma, in contrast to the slight effect on normal plasma as seen in Table 1, offers therefore a new test for the diagnosis of true hemophilia. It is interesting that if oxalated hemophilic plasma is allowed to stand several hours, the clotting time after the addition of calcium approaches normal. This further suggests that no essential factor is lacking, but that the defect lies in the slow liberation of thromboplastin from the platelets.

TABLE 1.—THE CLOTTING TIME OF RECALCIFIED OXALATED PLASMA AS A TEST FOR HEMOPHILIA.

		Coagulation time.		
			Recalcified plasma.	
		Lee White method, min.	After low centrifugation, sec.	After high centrifugation, sec.
Normal:	I	6	90	105
	II	6	125	145
	III	5	105	130
Hemophilia:	I	38	180	630*–1080†
	II	22	165*–195†	480*–660†
	III	..	180	330
	IV	40	165*–200†	300*–600†
	V	73	540	900
			180‡	180‡

* Beginning of coagulation.
† Formation of a firm clot.
‡ After standing 6 hours.

The following simple experiments illustrate plainly that hemophilic blood is normal in all respects except for the slow liberation of thromboplastin.

Patient, a white boy age 4. Definite family history of hemophilia.

Clotting time by Lee White Method: 1 hr. 13 min.
Clotting time by Lee White Method in a collodion coated test-tube: 7 hrs.

Experiment 1.

(*a*)		(*b*)	
Oxalated hemophilic plasma	0.1 cc.	Oxalated normal plasma	0.1 cc.
Thromboplastin	0.1 cc.	Thromboplastin	0.1 cc.
Calcium chloride 0.025 M.	0.1 cc.	Calcium chloride	0.1 cc.
Clotting time	12 sec.	Clotting time	11½ sec.

Experiment 2.

(*a*)		(*b*)	
Hemophilic plasma	0.1 cc.	Hemophilic plasma	0.1 cc.
Saline solution	0.1 cc.	Calcium chloride 0.025 M.	0.1 cc.
Thromboplastin	0.1 cc.	Thromboplastin	0.1 cc.
Clotting time	11½ sec.	Clotting time	14 sec.

Experiment 3.

(*a*)		(*b*)	
Hemophilic plasma	0.1 cc.	Hemophilic plasma	0.1 cc.
Saline solution	0.2 cc.	Calcium chloride 0.0125 M.	0.2 cc.
Clotting time	30 min.	Clotting time	13 min.

The first result to be observed is the clotting time. In a glass tube coagulation occurred in a little more than an hour, while in a collodion-coated tube, the time was 7 hours. It has been observed by both Dr. Hirschboeck[7] and myself that collodion behaves somewhat like the endothelial lining in preserving the fluidity of the blood, *i. e.*, by preventing the liberation of thromboplastin from platelets.

Experiment 1, which is really the quantitative measurement of prothrombin, shows that hemophilic plasma clotted as rapidly as the normal specimen when excess thromboplastin is present thus indicating that the prothrombin is normal. This the author with Stanley-Brown and Bancroft[13] had shown previously.

In Experiment 2*a*, the hemophilic plasma containing no added anticoagulant was treated with thromboplastin in the same manner as in Experiment 1 except that no calcium chloride was added. Coagulation occurred in 11½ seconds which agrees with the values obtained in the previous experiment. Obviously, the calcium of the blood is adequate and reactive. When, however, calcium was added to the plasma, the clotting time was prolonged showing that excess calcium has a depressing action on coagulation as was pointed out by the author[12b] previously.

In Experiment 3*a*, the hemophilic plasma was diluted with 2 volumes of physiologic saline solution with the result that coagulation which for the undiluted plasma was 73 minutes was reduced to 30 minutes. Significantly when the plasma was diluted with a weak solution of calcium chloride, clotting occurred in 13 minutes. This finding agrees with the observation of Ferguson[4] that osmotic disturbances within the platelet are under the specific influence of the calcium ions. Thus ionic calcium exerts two diametrically different influences on the speed of coagulation. It depresses the conversion of prothrombin to thrombin, but accelerates the liberation of thromboplastin from the platelets.

On the basis of the concept that hemophilia is basically a disease in which the platelets are abnormally stable, as these simple experiments indicate, an outline for diagnosis by means of laboratory tests can be offered.

Coagulation Time. The Lee White test is the most satisfactory. Clotting times on capillary blood are less delicate since in obtaining the blood a certain amount of contamination with thromboplastin from tissue juices is unavoidable. The clotting time is prolonged in hemophilia, but it varies greatly and may at times approach normal.

The prolonged coagulation time differentiates hemophilia from pseudohemophilia, hemorrhagic purpuras, and scurvy.

Delayed clotting is also found in the prothrombinopenia of obstructive jaundice and of the newborn, in fibrinogenopenia, in anaphylactic shock, and occasionally in severe cytopenic purpura.

Clotting Time of Recalcified Plasma. The test described in this paper is especially useful in doubtful cases of hemophilia. The marked effect of centrifuging on the clotting time, and the gradual decrease in the rate when plasma is allowed to stand can be considered strong positive evidence for hemophilia.

Prothrombin Concentration. The author's quantitative method for prothrombin[12a] is both simple and accurate. The prothrombin

is normal in hemophilia, but after severe bleeding may become somewhat decreased (rarely below 70%).

A normal concentration of prothrombin differentiates hemophilia from the various types of hypoprothrombinemias and from fibrinogenopenia.

Bleeding Time. The method of Duke, which is in common use, is satisfactory. Care must be taken not to make the cut too deep for fear of striking a large vessel since the test is designed essentially to determine the response of capillaries to the injury from the cut. The bleeding time in hemophilia is normal. Too deep a gash may however cause a false prolonged bleeding time due to the escape of blood from a larger vessel rather than from capillary oozing.

A normal bleeding time differentiates hemophilia from the hemorrhagic purpuras and from pseudohemophilia.

Clot Retraction. Although coagulation is prolonged in hemophilia, when it does occur, the clot undergoes retraction in the normal time of 30 to 60 minutes.

Normal syneresis distinguishes hemophilia from the hemorrhagic purpuras.

Tourniquet Test (Rumpel-Leede or Hess). In hemophilia the tourniquet test is negative, which means that no capillary erythropermeability exists. Since this test is exceedingly useful for recognizing all types of purpuric states, as Madison and Squier[10] have pointed out, its value in differential diagnosis is apparent.

Platelet Count. The number of platelets in uncomplicated hemophilia is well above 100,000 and usually is normal. The platelet count is of limited value, however, since no decrease occurs in pseudohemophilia and in many cases of purpura.

The blood of a true case of hemophilia should show the following:

1. Coagulation time (Lee White test), over 8 minutes (at 37½° C.).
2. Coagulation time of recalcified plasma:
   a. High speed centrifugation, over 5 minutes.
   b. Low speed centrifugation, over 3 minutes.
   c. Clotting time should decrease on standing.
3. Prothrombin concentration (Quick's method), above 70%.
4. Bleeding time (Duke's method), not over 4 minutes.
5. Clot retraction, not over 60 minutes after coagulation occurs.
6. Tourniquet test (Rumpel-Leede technique), not over 4 petechia in specified area.

By means of these simple laboratory tests a positive diagnosis of hemophilia can readily be made. In the typical case with a definite family history, the coagulation time will often suffice. It is the sporadic cases, the female bleeders, and those with a family history of transmission through both male and female progenitors that demand careful study. With a group of tests serving as a criterion for true hemophilia, an improvement in the accuracy of reported cases should be obtained.

With a sharper delineation of the hemorrhagic diseases, more attention should be given to the syndrome which is recognized by the name pseudohemophilia. This condition like hemophilia is hereditary, but in terms of the Mendelian law behaves as a sex-linked dominant factor, whereas in hemophilia the inherited factor is recessive. The disease is transmitted both by males and females and appears in its active form in both sexes. Coagulation time is normal but the bleeding time is intermittently prolonged. Clot retraction is normal, the platelets are not decreased, and the tourniquet test is negative. The first definite description of this disease was made in 1926 by Willebrand,[14] and from the reports that have since appeared, one can conclude that the condition is not uncommon.

Summary. The clotting time of recalcified plasma has been developed into a test for hemophilia. The coagulation time of oxalated hemophilic plasma subjected to high centrifugation is markedly longer than slowly centrifuged plasma. Such a marked difference is not obtained with normal blood.

A simple outline for the differential diagnosis from the other hemorrhagic diseases is outlined. It is based on the facts that in hemophilia the coagulation time of the blood and of the recalcified oxalated plasma is prolonged, but that clot retraction, bleeding time, prothrombin concentration, and the tourniquet test are normal.

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INFECTIOUS MONONUCLEOSIS—A DIAGNOSTIC PROBLEM.

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Infectious mononucleosis has been known as a clinical entity since 1889, when Pfeiffer[6] described it under the name of "glandular fever." The practitioner, however, is not always aware of its rela-

tively frequent occurrence or of the severe clinical picture with which this disease may manifest itself. Consequently, some cases of infectious mononucleosis are diagnosed as other infectious diseases, or as common acute infections of the oral cavity. The severe pharyngitis in infectious mononucleosis is the usual source of error, as it often simulates diphtheria.

To illustrate the diagnostic difficulties in some cases of infectious mononucleosis we present here an analysis of 21 cases which were referred with mistaken diagnoses to this hospital during the years 1937–1939.

The 21 cases were referred with the following diagnoses: Diphtheria or observation for diphtheria, 15; epidemic parotitis (mumps), 2; follicular tonsillitis, 2; streptococcal pharyngitis, 1; acute sinusitis, 1.

TABLE 1.—CASES OF INFECTIOUS MONONUCLEOSIS REFERRED OR ADMITTED WITH MISTAKEN DIAGNOSIS.

Case.		Name.	Sex.	Age.	Referred diagnosis.	Admission diagnosis.	Diphtheric antitoxin.	Diphtheria bacilli.		Heterophil antibodies, plain absorption.	Total days' illness.
								Culture.	Toxicity.		
1	6159	A. S.	M	14	Diphtheria	Follic. tonsill.	Yes	Neg.	N.d.*	1:224 –1:112	13
2	5329	S. G.	M	16	Observ. diph.	Follic. tonsill.	No	Pos.	Neg.	1:448 –1:224	16
3	5932	E. F.	M	23	Observ. diph.	Follic. tonsill.	No	Neg.	N.d.	1:996 –1:448	14+
4	5316	M. W.	F	15	Diphtheria	Diphtheria	Yes	Neg. (nose)	N.d.	1:224 –1:112	17
5	5221	D. S.	F	11	Observ. diph.	Diphtheria	Yes	Pos.	Neg.	1:224 –1:112	15
6	5288	R. C.	M	4	Diphtheria	Diphtheria	Yes	Pos.	Neg.	1:112 –1:56	19
7	1244	H. F.	M	25	Str. pharyng.	Infect. mononucl.	No	Neg.	N.d.	1:56 –1:56	18
8	619	C. Y.	F	21	Diphtheria	Diphtheria	Yes	Neg.	N.d.	1:112 –1:56	18
9	5572	W. M.	M	3	Diphtheria	Str. tonsillitis	Yes	Neg.	N.d.	1:112 –1:56	13
10	5298	R. F.	M	28	...	Acute sinusitis	No	Neg.	N.d.	1:448 –1:224	12
11	4975	R. R.	M	11	Observ. diph.	Infect. mononucl.	No	Neg.	N.d.	1:3584–1:1792	17
12	4639	I. G.	F	16	Diphtheria	Infect. mononucl.	Yes	Neg.	N.d.	1:1792–1:896	18
13	4382	B. N.	M	8	Epi. parotitis	Infect. mononucl.	Yes	Pos.	Neg.	1:56 –1:56	20
14	537	M. M.	F	36	Diphtheria	Infect. mononucl.	No	Neg.	N.d.	1:112 –1:56	28
15	276	N. K.	F	24	Diphtheria	Str. tonsillitis	Yes	Pos.	Neg.	1:112 –1:56	19
16	689	M. S.	F	20	Observ. diph.	Acute tonsillitis	No	Neg.	N.d.	1:224 –1:112	10
17	2433	A. V.	F	20	Epi. parotitis	Observ. parotitis	No	Neg.	N.d.	1:224 –1:112	11
18	2968	E. S.	F	21	...	Acute tonsillitis	No	Neg.	N.d.	1:896 –1:896	16
19	2718	Ad. S.	F	3½	Diphtheria	Diphtheria	Yes	Neg.	N.d.	1:28 –1:14	24
20	3481	L. C.	F	25	...	Acute tonsillitis	No	Pos.	Neg.	Negative	20
21	4133	H. S.	M	23	Diphtheria	Septic sore throat	Yes	Pos.	Neg.	1:1792–1:896	28

* N.d. signifies not done.

In 14 cases the clinical picture was considered sufficiently suspicious of diphtheria to warrant the administration of diphtheria antitoxin upon admission, without awaiting confirmation by culture of the presence of the diphtheria bacillus in the throat. The diagnostic difficulty was further complicated in 7 of these cases by the presence of non-toxic diphtheria-like bacilli in the throats of 6 patients and in the nose of 1 patient. The negative toxicity tests on the isolated bacilli, the hematologic picture, the positive heterophil antibody test and the lack of response to the diphtheria antitoxin helped in establishing the correct diagnosis.

In 5 cases the diagnosis of infectious mononucleosis was made upon admission on a basis of physical findings of pharyngitis with extensive membranous exudate and enlargement of several groups of lymph nodes. The diagnosis was later confirmed by hematologic and serologic findings.

Adequate descriptions of infectious mononucleosis have appeared repeatedly in the literature, and a complete review of the subject was made recently by Bernstein.[1] However, the observations on the 21 cases of this series present some additional clinical and laboratory data of practical significance.

Distribution. 1. *Age.* The youngest patient in this series was 3 years old; the oldest 36 years. The age incidence showed a greater proportion of young adults than children (7 cases between the ages of 3 to 14; 14 cases between the ages of 15 to 36).

2. *Sex.* Although the greater susceptibility of males is mentioned by several authors quoted by Bernstein, the cases in our series were equally distributed between the sexes (10 males, 11 females).

3. *Color.* Four patients in this series were negroes. According to Bernstein, only 1 case of infectious mononucleosis in negroes had been reported in the literature by Longcope.[4]

4. *Regional.* The 4 negro patients who were seen during a single month came from the same district of the city; we were unable to establish any contacts between them, however.

Clinical Picture. The clinical picture of infectious mononucleosis, with special emphasis on the appearance of the throat is presented in some detail, as familiarity with the clinical manifestations often makes diagnosis possible before the laboratory tests are completed.

Duration of Illness. Duration of illness prior to admission to the hospital varied from 1 to 22 days; hospitalization from 6 to 24 days. The total days of illness ranged from 10 to 28.

Subjective Findings. On admission the complaints were: pharyngitis, 20; malaise, 9; anorexia, 8; headache, 7; dysphagia, 8; vomiting, 2; facial edema, 2; lacrimation, 2; chills, 2; nasal discharge, 2; dysarthria, 2.

Objective Findings. The temperature on admission ranged from 99° to 104° F. The duration of the fever varied from 7 to 17 days following the onset of illness. The pulse was elevated in relation to the temperature.

The physical findings are as follows: Tonsillitis: membranous, 20; non-membranous, 1. Lymphadenitis: cervical, 20; axillary, 10; inguinal, 10; popliteal, 2. Palpable spleen, 7. Palpable liver, 3. Edema of the face, 2. Dacryocystitis, 1.

The tonsillitis was the most constant finding. On admission all patients with one exception presented a membrane or an exudate on one or both tonsils. In 18 cases the tonsillitis was considered severe.

In patients severely ill the tonsils were extremely large, almost

meeting in the midline. The membrane or exudate varied in color from ivory-white and grayish white, to grayish yellow. It was adherent to the tonsil and could not be easily removed. In many instances the membrane was granular in appearance, resembling the head of a cauliflower, or a mulberry. The mucosa of the hard palate, the pillars and the fauces in cases with this type of exudate presented a wrinkled, corrugated appearance which is frequently seen in pharyngitis caused by the staphylococcus. The mouth appeared dry, parched, and was glazed with thick, tenacious mucus. In some patients only the tissues immediately surrounding the tonsils were inflamed. With the onset of defervescence the tonsillar exudate loosened up and generally came off *en masse*.

Nine patients showed enlargement of the cervical, axillary and inguinal lymph nodes; in 2 cases the popliteal lymph nodes were also enlarged.

The spleen was palpable in 7 cases. It was firm, not tender and not markedly enlarged. The liver was palpable in 3 cases, and was not tender.

Edema of the face was observed in 2 patients.

Complications. One patient developed dacryocystitis on 9th day of illness.

Secondary anemia developed in 1 case on the 11th day of illness. The patient received no drugs.

No nephritis, jaundice, abdominal pain, purpura or cerebral complications were observed in this series.

Laboratory Findings. *Hematologic.* High total white cell counts of 20,000 or over were observed in 7 patients, the highest total count being 27,800. Four of the 7 patients were children aged 3 to 14 years. In the 4 children the high total white cell counts occurred in the 1st, 3d, 5th and 6th days of illness; in the 3 adults on the 10th, 11th and 12th day of illness. In individual cases the highest total white blood cell counts followed the same pattern: below the age of 15 the highest total counts occurred during the 1st week of illness; in adults who were in the hospital during the 1st and 2d week of illness the highest total counts were observed during the 2d week.

The blood smears were stained with the MacNeal tetrachrome stain which permits an adequate differentiation of monocytes from abnormal large lymphocytes. Duplicate smears were stained with the Goodpasture peroxidase stain, often with subsequent staining of the same slide with the tetrachrome, in order to bring out the peroxidase positive granules of the monocytes.

The highest percentage of lymphocytes found in this series was 87%, in an 11-year-old child, on the 8th day of illness. The highest absolute number of lymphocytes observed per 1 c.mm. was 17,675 (75% lymphocytes), in an adult, on the 12th day of illness. The highest percentage of abnormal lymphocytes (45%) with amitotic

division of lymphocytes in the peripheral blood, was seen on the 10th day of illness in an adult who had 61% of total lymphocytes.

The "shift to the left" and the occurrence of toxic granules in the neutrophils was more pronounced in children than in adults.

Secondary anemia developed in 1 patient who received no drugs while in the hospital (Case R. C.). On the 6th day the blood count showed 4,700,000 red blood cells and 75% hemoglobin. On the 11th day his red blood cells fell to 3,180,000, the hemoglobin was 55%, and nucleated red blood cells appeared in the smear. This was the patient with the highest white cell count in this series (27,800).

Serologic. The heterophil antibody test was performed by the Davidsohn method[3a,b] in preference to the original technique of Paul and Bunnell.[5] The highest level of agglutination was controlled microscopically, by examining a drop of the suspension on a slide (without a cover) with a low power objective. The differential method of Davidsohn was adapted because the majority of our patients with infectious mononucleosis received the horse serum in the form of diphtheria antitoxin. Consequently there was a possibility of the presence of Forssman antibodies in their blood, either from the horse serum in their blood stream, or as a result of serum sickness. Absorption of Forssman antibodies by the suspenison of guinea-pig kidney, as recommended by Davidsohn, eliminates entirely the Forssman antibodies from the blood serum, but removes only a part of the heterophil antibodies. The agglutination titer was 1:56 (with a drop to 1:28 after absorption) was considered positive.

Bernstein pointed out that the titer of heterophil antibody does not change after administration of horse serum. One of our patients (B. N.) showed a titer of 1:56, and no absorption by the suspension of guinea-pig kidney suspension; after administration of diphtheria antitoxin the titer remained unchanged.

The heterophil antibody reaction was positive in 19 of our 21 cases (90%), negative in 1 (adult) and doubtful in 1 (child, Ad. S., titer 1:28 with a drop to 1:14 after absorption). The high percentage of positive reactions in our series corresponds to the findings of Bernstein (92% of positive reactions). Other authors observed a lower incidence of positive heterophil antibody reactions in infectious mononucleosis (Rosenthal and Wenkebach[7]).

The heterophil antibody reaction usually becomes positive during the 1st week of illness (Bernstein). In 1 of our cases it was found to be positive on the 2d day of illness, the titer (1:56) remaining unchanged on the 4th and 5th day. In another case, however, the reaction was negative on the 7th day, but became positive (1:112) on the 8th day. The height of the titer in individual cases was usually reached during the first week of illness. However, in 1 case the titer which was 1:56 on the 6th day rose to 1:224 on the 9th day.

The highest titer observed in this series was 1:3584, in a boy of 11, on the 8th day of illness.

We can confirm the observation of Bernstein that the titer of a positive serum stored in an icebox remains unchanged for months. Positive sera thus may be kept in storage and used as control in performing the heterophil antibody test with unknown sera.

False positive Wassermann and Kline reactions were observed in 4 cases with no history or clinical findings suggestive of syphilis. In these cases subsequent tests showed either negative results within a few days, or less sensitive reactions became negative, while the more sensitive reactions still showed positive results at the time the patients were discharged from the hospital.

Case	Age	Day of illness	Test	Day of illness	Test
H. P.	25	11	Wassermann: Alcohol. antig. 0 Cholest. antig. ± Kline diagn. positive	17	 Kline diagn. ±
M. W.	15	5	Wassermann: Alcohol. antig. 3+ Cholest. antig. 4+ Kline diagn. } Strongly Kline exclus. } positive	17	 All tests negative
Ad. S.	3½	7	Wassermann: Alcohol. antig. 1+ Cholest. antig. 2+ Kline diagn. } Positive Kline exclus. }	22	 All tests negative
H. S.	23	5	Wassermann: Alcohol. antig. 3+ Cholest. antig. 4+ Kline diagn. } Strongly Kline exclus. } positive	17	Wassermann: Alcohol. antig. 0 Cholest. antig. 2+ Kline diagn. } Positive Kline exclus. }

There was no correlation between the titer of the heterophil antibody reaction and the presence of false-positive reactions for syphilis.

Bacteriologic. Throat smears were examined for Vincent's spirilli and fusiform bacilli in 15 cases. Scattered Vincent's microörganisms were found in 6 cases. Only 1 of the patients (M. W.) showing the presence of spirilli had false-positive Wassermann and Kline reactions.

Non-toxic bacilli of the diphtheria group were found in 7 cases (6 in the throat, 1 in the nose). Their presence delayed the correct diagnosis until the completion of the toxicity tests.

Other bacteria cultured from the throat were *Strep. hemolyticus*, *Strep. viridans*, *Staph. aureus* and *Staph. albus*.

Differential Diagnosis. The diagnosis of infectious mononucleosis is not difficult, if the possibility of that disease is kept in mind. While the clinical picture may not always be typical, a hematologic study over a period of several days, and a positive heterophil antibody reaction helps to confirm the diagnosis.

Since the infectious mononucleosis is primarily a pharyngeal infec-

tion, the differential diagnosis must include: *a*, diphtheria, *b*, acute tonsillitis, *c*, ulcerative sore throat (superficial and Vincent's angina), *d*, streptococcus pharyngitis, *e*, staphylococcus pharyngitis, *f*, agranulocytic angina, and, *g*, acute lymphatic leukemia with pharyngitis.

In view of widespread lymphadenopathy, acute lymphatic leukemia must be considered. In the early stages of infectious mononucleosis, when only the cervical lymphadenitis may be markedly enlarged the question of mumps may arise, as the enlarged cervical lymph nodes may simulate the enlargement of the parotid glands.

Diphtheria. Early differentiation from diphtheria is especially desirable, in order to avoid administration of the antitoxin and sensitization of the patient to the horse serum.

The typical appearance of the throat in diphtheria, with its adherent grayish membrane, is well known. On removal the membrane leaves a bleeding surface. However, in atypical cases the diagnosis is at times very difficult without bacteriologic confirmation. If the patient's general condition permits a delay in the administration of the antitoxin, a throat smear may be examined for the presence of the diphtheria bacilli, and rapid cultures (the 4-hour method of Brahdy, Lenarsky, Smith and Gaffney[2]) for the presence of the diphtheria bacilli may be done before the administration of the antitoxin. However, if the patient presents a clinical picture suggestive of toxic diphtheria, no time should be lost in the administration of the antitoxin, and all the laboratory work may be done later.

If diphtheria-like bacilli are found in the throat or nose cultures in a patient who does not respond to the antitoxin, the isolated bacillus must be tested for toxicity and the possibility of infectious mononucleosis must be considered. The diagnosis can usually be made by hematologic and serologic examinations before the completion of the toxicity test. The blood picture in diphtheria is usually one of neutrophil leukocytosis. However, abnormal lymphocytes occur occasionally in children. The heterophil antibody reaction is negative despite the administration of the antitoxin, if the differential method of Davidsohn is used.

Two typical cases of infectious mononucleosis referred to the hospital with the diagnosis of diphtheria are presented.

Case Reports. CASE 1.—W. M. (5572.) *Referred as diphtheria. Throat culture negative for diphtheria bacilli.* The patient, a 3-year-old white male, was admitted on the 4th day of illness complaining of fever, anorexia, pains in the joints and sore throat. The admission diagnosis was: Streptococcus tonsillitis; possible diphtheria. The temperature on admission was 103.4° F.; pulse, 140. The patient was acutely ill, with rapid respirations, flaring alæ nasæ and oral fetor. The tonsils were large, severely inflamed and covered with a thick grayish yellow plastic exudate. The exudate was present also over the posterial pharyngeal wall. There was a moderate serous nasal discharge. The lids of both eyes were mildly edematous, tender and puffy.

The cervical, axillary and inguinal lymph nodes were enlarged and discrete. The liver was palpable—1 finger below the costal margin, but the

spleen was not palpable. The patient received 20,000 units of diphtheria antitoxin and, in addition, 6000 units of scarlet fever antitoxin.

On the 5th day of illness, the membrane persisted.

On the 6th day of illness, the spleen was palpable and the appearance of the throat and of the tonsillar membrane was somewhat improved. The blood count showed 22,600 white blood cells with 32% neutrophils and 66% lymphocytes, of which 52% were abnormal. The heterophil antibody test was positive 1:112 (after absorption—1:56).

On the 10th day of illness, the left tonsil showed a crater-like excavation, covered with a yellowish membrane.

On the 11th day of illness, the cervical lymph nodes were no longer palpable. The axillary and inguinal nodes were still present. On the 12th day of illness, the tonsils no longer showed evidence of an exudate.

The temperature returned to normal by lysis on the 13th day of illness.

CASE 2.—R. C. (5288.) *Referred as diphtheria. Non-toxic diphtheria-like bacilli in the throat. Secondary anemia in the course of infectious mononucleosis.* The patient, a 4-year-old colored child, was admitted on the 5th day of illness, as a case of diphtheria. The complaints were: sore throat, headache, fever and dysphagia. On admission the temperature was 103.2° F.; pulse, 136. The patient was undernourished, underdeveloped and acutely ill. Both tonsils were very large, inflamed and covered with a thick gray foul-smelling membrane, adherent to the substance of the tonsil. There was a bleeding when the membrane was removed. The cervical and inguinal lymph nodes were enlarged. The patient was given 20,000 units of diphtheria antitoxin. The blood count on admission showed 27,800 white blood cells with 57% lymphocytes.

On the 6th day of illness, there was no response to the antitoxin. A blood count showed hemoglobin, 75%, and red blood cells, 4,970,000. The throat culture taken on the preceding day showed the presence of diphtheria-like bacilli (the bacilli were subsequently found to be non-toxic). The heterophil antibody reaction was positive 1:112 (after absorption—1:56).

On the 8th day of illness, the left tonsil showed a deep ulceration with a sharp line of demarcation against normal tonsillar tissue. A blood count showed 17,000 white blood cells, with lymphocytes 54%, of which 13% were abnormal.

On the 9th day of illness, the throat began to clear. The temperature became normal and the membrane had completely disappeared by the 12th day of illness.

On the 11th day of illness, the hemoglobin was 55%, red blood cells, 3,180,000, with normoblasts in the smear. The patient received no drugs while in the hospital. Blood transfusions were given.

Acute Follicular Tonsillitis. In early stages of infectious mononucleosis the exudate may be follicular in character (Case B. N.). The differentiation from the acute follicular tonsillitis is possible only with the aid of blood studies.

Ulcerative Stomatitis. 1. *Superficial.* Superficial ulcers are present on the swollen tonsils, often on the soft palate and in the pharynx. An exudate or a membrane may be present. The blood count is within normal limits.

2. *Vincent's Angina.* One or both tonsils may be covered with a grayish white or dirty-yellow exudate often superimposed on a slough. A clear-cut ulcer remains after the separation of the slough. The diagnosis is established by the finding of numerous spirilli and fusiform bacilli in smears from the throat. The Wassermann and

Kline reactions may be positive, but the heterophil antibody reaction is negative. The blood morphology shows no deviation from normal.

Streptococcal and Staphylococcal Pharyngitis. In both types of infection a thick, yellowish or whitish-gray exudate may be present over the tonsils, soft palate and posterior pharyngeal wall. In our experience, in the staphylococcus infection the exudate may be granular, mulberry-like, and resembles particularly the exudate in infectious mononucleosis.

A neutrophil leukocytosis is present in both streptococcus and staphylococcus pharyngitis.

Agranulocytic Angina. The tonsils present a dirty-gray or blackish appearance, as if covered with a membrane. This appearance is, however, due to necrosis of the substance of the tonsils and not to a superimposed exudate. The posterior pharyngeal wall and the larynx may present a similar appearance. A history of medication injurious to the hemopoietic system can often be elicited. The diagnosis is established by a blood count showing leukopenia with neutropenia.

Acute Lymphatic Leukemia, With or Without Pharyngitis. The differential diagnosis may be difficult, as a widespread lymphadenopathy and abnormal lymphocytes in the blood may be present in both lymphatic leukemia and infectious mononucleosis. The heterophil antibody reaction is negative in acute lymphatic leukemia, although it has been reported to be positive in a case of aleukemic leukemia (Paul and Bunnell[5]). Examination of bone marrow may be necessary, if the heterophil antibody reaction is negative.

Epidemic Parotitis.—The differentiation of infectious mononucleosis from the epidemic parotitis is facilitated by the presence of widespread lymphadenopathy and by the positive heterophil antibody reaction.

A case of infectious mononucleosis referred to the hospital with the diagnosis of mumps is presented.

CASE 3.—B. N. (4382.) *Referred as epidemic parotitis. Non-toxic diphtheria-like bacilli in the throat.* The patient, an 8-year-old white male, was referred to the hospital as a case of epidemic parotitis, on the 1st day of illness. The complaints were: a swelling over the left side of the face and a moderate epistaxis that morning. On admission the tonsils were enlarged and presented a white follicular exudate. The pharynx was inflamed, and oral fetor was present. The anterior and posterior cervical lymph nodes were enlarged on both sides, with swelling below and behind the angle of the jaw on the left. The parotid gland was not definitely involved. The axillary and inguinal lymph nodes were palpable. The edge of the spleen was palpable. A soft systolic apical murmur was auscultated. The temperature was 104°, pulse, 124. A tentative diagnosis of infectious mononucleosis was made.

The blood count done on the same day showed 20,750 white cells with 73% lymphocytes and 27% neutrophils. The heterophil antibody tests on the 2d and 4th days of illness were positive 1:56, with no change of the titer after absorption.

The swelling of the left side of the face during the 2d and 3d days of illness increased.

On the 4th day of illness throat cultures for diphtheria-like bacilli were positive. The Schick test was negative. Because of the spread of the exudate on the right tonsil and the toxic state of the patient, 20,000 units of diphtheria antitoxin were given.

The blood count on the 5th day of illness showed 11,500 white cells, 65% lymphocytes, of which 49% were abnormal. The heterophil antibody test remained unchanged.

On the 6th day of illness the facial swelling began to decrease and the exudate on the tonsil began to peel away. The general condition improved rapidly.

Subsequent examination showed that the diphtheria-like bacilli from the throat were non-toxic. The patient was discharged on the 16th day of illness with complete subsidence of adenopathy.

Conclusions. 1. Patients with infectious mononucleosis often are severely ill. An extensive pharyngitis is usually present, often simulating diphtheria.

2. Cervical lymphadenopathy in early infectious mononucleosis may occasionally simulate mumps.

3. Early differentiation of infectious mononucleosis from diphtheria is desirable in order to avoid unnecessary administration of diphtheria antitoxin and sensitization of the patient to horse serum.

4. Cases of clinical diphtheria which do not respond to antitoxin must be investigated hematologically and serologically for the possibility of infectious mononucleosis.

5. Non-toxic diphtheria-like bacilli may be present in the nose and throat of patients with infectious mononucleosis.

6. In children the highest white blood counts are observed during the 1st week of illness, in adults in the 2d week of illness.

7. The heterophil antibody reaction was positive in 90% of 21 patients of this series.

8. The titer of sera showing positive heterophil antibody reactions remains constant for months, if the sera are stored in an icebox. Positive sera may be used as control in performing the test with unknown sera.

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OBSERVATIONS ON INFECTIOUS MONONUCLEOSIS.

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During the course of our efforts to determine the mechanism of infectious mononucleosis, we have encountered certain interesting phenomena which we propose to discuss here. They concern the

two characteristic features of this disease; the hematology and the serology. These manifestations alone differentiate the entity of infectious mononucleosis from others presenting a similar clinical picture. Obviously then, investigations concerning these aspects of the illness are indicated in the attempt to ascertain its nature.

It is generally held that the hematologic and serologic findings in infectious mononucleosis are pathognomonic. However, a few previously recorded observations may seem contrary to this opinion. On one hand, the incidence of positive Paul-Bunnell reactions associated with the typical lymphocytic picture has not been 100%. Thus Paul[13] found the test positive in 90% of a series of 50 cases and Rosenthal and Wenkebach[16] found only 50% to be positive. Several reasons for these results might be possible: *a*, faulty serologic technique; *b*, failure to make serial heterophil determinations and thus miss the appearance of the antibodies; *c*, improper interpretation of the differential count. Whatever the reason, the failure to obtain a positive heterophil reaction when the typical cells of infectious mononucleosis are found has given rise to the hypothesis that one may be dealing with an entity separate from infectious mononucleosis.

On the other hand, there are several cases in the literature[4,7,14,24] in which the heterophil antibodies were increased without clinical or hematologic evidence of infectious mononucleosis. But as the differential adsorption tests with guinea-pig kidney or beef erythrocytes were not done in some instances, the antibodies were not conclusively proven to be those of infectious mononucleosis. The 2 cases of this nature presented by Stuart *et al.*[24] were shown to have the typical antibodies during recovery from meningococcal meningitis which had been treated with immune horse serum. Serum sickness with its characteristic heterophil antibody had also appeared in both patients prior to the development of those of infectious mononucleosis. One of these cases had some form of an intercurrent infection on the day the complete Paul-Bunnell test was positive. Such an event during the course of infectious mononucleosis has been shown to obliterate the blood picture of this disease.[9,11,12] Hence, for all practical purposes, a positive Paul-Bunnell test is always associated with characteristic lymphocytes.

The question remaining is then, does the presence of these abnormal cells without an elevated heterophil titer indicate infectious mononucleosis? Are they a reflection of a previous episode of this disease, for Farley[10] found them to be present 10 years after the acute stages had subsided in 1 case. Or are these cells an "irritation" form of lymphocyte which are liberated into the blood stream under certain conditions? We shall return to these questions after the presentation of our data.

Material and Methods. Blood counts and blood for the heterophil test were obtained as soon as possible from the college students on their appear-

ance at the college dispensary with suggestive signs and symptoms. These tests were repeated as frequently as practical under these conditions. The differential counts were performed by the author. The heterophil tests were made in two laboratories: those in which hot and cold titers are recorded, were done at the laboratory of the State of Connecticut; the remainder at the New Haven Hospital. The majority of heterophil tests were performed in the former laboratory as differential adsorptions could be done there. The reciprocals of the dilutions are recorded in the following tables. It has been shown that the increased heterophil antibodies of infectious mononucleosis are not adsorbed by tissues containing the Forssman antigen such as guinea-pig kidney; whereas the true Forssman antibody and the heterophil antibody of serum sickness are adsorbed by such tissues.

Results. The cases have been segregated into three classes for obvious reasons. The first group consists of patients who presented the clinical findings of infectious mononucleosis but who lacked an heterophil response of any significant degree. An absolute lymphocytosis is to be noted in each case and the number of abnormal forms is in general less than the figures recorded in the other groups.

GROUP I.

	Day of disease.	W.B.C.	P.	L.	Abn. L	M.	E.	B.	Paul-Bunnell.	
J.S.	4	11,000	80	16	0	3	1	0		
	5	9,700	60	37	3	3	0	0		
	6	8,400	53	37	18	4	6	0	H.(−): C.(−)	
	8								H.(−): C.3+ 10;1+ 40	
	10	12,000	48	41	17	5	6	0		
	17								H.(−): C.4+ 10;2+ 20	
	30	9,000	64	29	0	4	3	0	H.(−): C.(−)	
E.D.	6	12,000	54	38	5	6	1	1	H.(−): C.4+ 10;3+ 40	
	9	14,100	51	45	15	4	0	0		
	12								H.(−): C.4+ 20;2+ 40	
	17								H.1+ 5: C.4+ 10;1+ 40	
	37		39	52	4	9	0	0	H.(−): C.3+ 10;1+ 20	
									Before adsorption with guinea-pig kidney.	After adsorption.
R.M.	6								H.4+ 10;3+ 20;2+ 40: C.4+ 20;3+ 40;1+ 80:	
	8	10,500	63	35	4	2	0	0		
	10	9,400	62	34	3	4	0	0		
	15	8,900	53	37	8	8	1	1	H.4+ 10;2+ 20;1+ 40: C.4+ 80;2+ 160:	(−) 2+ 5;1+ 10:
	22								H.4+ 10;3+ 20;1+ 40: C.4+ 80:	(−) 1 + 5:
R.S.	3	13,000	66	20	5	12	1	1		
	4								H.2+ 5;1+ 10: C.4+ 10;3+ 20;1+ 40:	
	14	10,800	35	60	25	4	1	0	H.3+ 5;1+ 10: C.4+ 80;1+ 160:	
	21	11,000	36	61	22	2	1	0	H.2+ 5;1+ 10: C.4+ 40;3+ 80;1+ 160:	

H. means hot titer; C. cold titer. Figures are the reciprocals of the serum dilutions.

R. S. was said to have had "glandular fever" exactly 2 years before this episode, but no blood count or heterophil test was done.

The adsorption test with guinea-pig kidney was performed in Group I on R. M. only, as the hot titers in the other instances were not elevated above normal values. The significance of the residual agglutinative activity of R. M.'s serum at 4° C. after adsorbing with guinea-pig tissue has not been determined.

The second group consists of 2 cases of infectious mononucleosis on which heterophil determinations were made very early in the course of the disease. The significant points in these cases are: 1, the increase of Forssman antibodies before the development of those of infectious mononucleosis; and 2, the greater percentage of abnormal lymphocytes than in the previous group.

GROUP II.

Day of disease.	W.B.C.	P.	L.	Abn. L.	M.	E.	B.	Paul-Bunnell. Before adsorption with guinea-pig kidney.	Paul-Bunnell. After adsorption.
H.D. 12	10,700	47	47	15	6	0	0	H.2+ 5;1+ 10	(−)
								C.4+ 10;2+ 20;1+ 40	(−)
18								H.3+ 5;2+ 20;1+ 40	(−)
								C.4+ 40;3+ 80	(−)
28	11,600	32	63	27	5	0	0	H.4+ 20;2+ 40:::	2+ 10;1+ 20
								C.4+ 20;2+ 160;1+ 320::	3+ 10;2+ 20; 1+ 40
C.A. 4	10,000	38	57	28	5	0	0	H.4+ 40;2+ 160:::	(−)
								C.4+ 40;2+ 320::	(−)
7								H.4+ 80;3+ 160;1+ 320:	4+ 80;1+ 320
								C.4+ 40;2+ 320::	4+ 40;3+ 320; 1+ 640
8	15,000	29	67	47	3	1	0		
15	14,500	30	66	36	4	0	0		
17								H.4+ 80;2+ 320	4+ 160;2+ 320
								C.4+ 160;3+ 320; 2+ 1280	4+ 320;2+ 640;3+ 2560

We reproduce the findings of the third group to afford some comparison with the above cited disclosures. In particular, one should note the higher percentage of abnormal lymphocytes than in Group I and the variable time of appearance of the heterophil antibodies from the onset of symptoms.

We have not included in this report our findings in a number of cases with upper respiratory infections, acute pharyngitis, or sinusitis, solely because serial blood counts and Paul-Bunnell reactions were not complete in these instances. However, 15 heterophil determinations were performed at various times during these afflictions and the results were all negative. A study of the blood smears from many of these cases showed clearly, on the other hand, cells characteristic of infectious mononucleosis which comprised 1% to 10% of the differential count. This observation confirms the similar findings of others.[2,8,24]

Discussion. Our data present two striking facts and provoke considerable speculation. If it is accepted that the curious lymphocytes of infectious mononucleosis are found in the circulation in health and other diseases, it is evident that a positive Paul-Bunnell reaction only occurs when these cells form a large proportion of the differential white count. Secondly, we confirm the observation of Sohier *et al.*[18] that the titer of the normal Forssman heterophil antibody may increase in infectious mononucleosis before the development of those heterophil antibodies typical of this disease. This

latter statement is perhaps not entirely justifiable, as we have been unable to test these sera with beef erythrocytes.*

GROUP III.

	Day of disease.	W.B.C.	P.	L.	Abn. L.	M.	E.	B.	Paul-Bunnell. Before adsorption.	Paul-Bunnell. After adsorption.
J.M.	8	13,750	36	50	11	10	4	0		
	10								+4	
	11	11,600	27	51	32	20	2			
	21								H.4+ 80;2+ 320:::	4+ 40;2+ 320
									C.4+ 160;2+ 640::	4+ 160;1+ 640
	93								H.2+ 5;1+ 10	
									C.4+ 10;1+ 40	
R.F.	8	10,000	53	43	40	3	1	0	H.4+ 40;3+ 80;2+ 160; 1+ 320:	3+ 10;2+ 20; 1+ 40
									C.4+ 160;2+ 320; 1+ 640:::	4+ 40;3+ 80; 2+ 160
	25	15,600	42	53	5	5	0	0		
	29								H.4+ 20;2+ 80;1+ 160:::	2+ 20;1+ 40
									C.4+ 80;3+ 160; 2+ 640; 1+ 1260:	4+ 40;3+80; 1+ 320
C.F.	18	25,000	7	91	76	0	2	0	H.4+ 10;3+ 40;2+ 80::::	4+ 160;2+ 320
									C.4+ 20;3+ 40;1+ 80:::	4+ 320;2+ 640
	47	14,200	44	48	4	6	2	0	H.2+ 5;1+ 20:	(−)
									C.4+ 5;3+ 10;2+ 40; 1+ 160	(−)
J.A.	5	6,250	60	34	3	6	0	0	+8	
	7	7,250	42	53	12	5	0	0		
	9								+128	
	10	14,350	7	88	67	5	0	0		
	14								+256	
	16	17,550	19	76	42	4	1	0		
E.C.	7	16,400	12	88	60	0	0	0	H.4+ 320;2+ 2560::	4+ 160;3+ 640; 2+ 1280; 1+ 2560
									C.4+ 2560:::	4+ 160;3+ 2560
	19	12,100	21	72	41	6	1	0	H.4+ 320;3+ 640; 1+ 1280::	4+ 320; 3+ 1280; 2+ 2560
									C.4+ 320;3+ 1280; 2+ 2560::	4+ 2560
C.E.	3	6,100	54	35	6	8	3	0		
	5	4,500	78	12	?	10	0	0	H.4+ 5;1+ 10	
									C.4+ 10;3+ 40;1+ 80:	
	7	4,800	58	32	12	10	0	0		
	9	15,000	10	80	?	10	0	0		
	15	8,900	11	84	38	3	0	2	H.4+ 10;3+ 40;2+ 80:	3+ 5;2+ 10; 1+ 40
									C.4+ 160;2+ 320:::	4+ 80;3+ 160; 1+ 320

The nature of the characteristic antibodies of infectious mononucleosis has been the subject of much argument. The investigations of several authors[1,3,6,19,20,24] present evidence that these immune bodies do not fulfill the requirements of the true Forssman heterophil antibody. The same has been shown to be the case for the increased heterophil antibodies of serum sickness[1,6,23] despite the fact that the injected sera almost always contain the Forssman

* A sample of C.A.'s serum withdrawn on the 4th day of disease, and which had been kept at 4° C. for 6 weeks, was sent to Dr. K. M. Wheeler of the Connecticut State Department of Health. He very kindly subjected the sample to various procedures which indicated beyond doubt that the antibodies were those of infectious mononucleosis and not of the Forssman type as we have described. This raises an interesting point—was the original serologic technique at fault or did this change occur *in vitro?* On this same day, 20 cc. of C.A.'s fresh whole blood was given intraperitoneally to a Macacus. No significant clinical, hematological or serological changes occurred in the monkey in 4 weeks.

antigen. Heterophil antibodies are also augmented in patients receiving immune horse serum who do not develop serum sickness.[5] Whether these antibodies are of the Forssman class is not known, as differential adsorption tests have never been reported in this connection. When rabbit serum, which does not contain the Forssman antigen, or horse serum from which this antigen has been removed are used, an elevated heterophil titer is produced.[15,17] Unfortunately again the differential adsorption tests have not been made. We think it is significant, however, that C. A. of Group II showed an increase of the heterophil antibodies adsorbable by guinea-pig kidney on the fourth day of illness; whereas 3 days later they were not.*

The whole question of antibody production in infectious mononucleosis is obscure and complex. Non-specific bacterial agglutinins for typhoid, paratyphoid, undulant fever, and so on appear from time to time. Falsely positive Wassermann, Kahn, and Eagle reactions are frequent. Two mechanisms for these findings may be postulated: 1, the antibodies may be those normally present or previously acquired in some manner; 2, the chemical and spatial structure of the antigens of the above conditions and infectious mononucleosis may be very closely related. Regardless of the means, the results are non-specific. With the former mechanism, a liberation of preformed antibodies could be thought to occur. In the second instance, either "typhoid-like" immune bodies might be produced by the antigen of infectious mononucleosis; or the heterophil antibody itself might be capable of agglutinating the bacteria and so on. Either mechanism could also explain the observation of the Forssman antibody in our cases.

What seems more logical, perhaps, is that the heterophil antibodies of infectious mononucleosis represent certain alterations in the molecular complex of the Forssman antibody. That is, the presence or development of the latter is essential for those of infectious mononucleosis. Davidsohn[5] has presented evidence that a similar state of affairs may determine the heterophil response to immune horse serum. Stuart *et al.*[21,22] likewise showed that the ability to produce specific human A agglutinins in rabbits depends upon the presence of preformed A agglutinins in their sera. Perhaps it is mere coincidence, but in the case of C. A. it should be noted that the heterophil titers before the adsorption tests were carried out are almost identical, although 3 days supervened between the titrations.*

Prior to the presentation of our data, we ended the introduction with some unanswered questions. We still feel unable to settle these queries conclusively. It is our personal opinion that the finding of abnormal lymphocytes in states without a positive Paul-Bunnell test does not indicate a previous state of infectious mononucleosis. Possibly, the cells are irritative in origin and appear in response to a variety of foreign proteins. Under certain conditions this reaction

* See footnote on preceding page.

may be exaggerated and the typical picture of infectious mononucleosis develops. Whether there is a direct connection between the curious cells and antibodies of the disease is a problem demanding investigation.

Summary. We have presented evidence of the following phenomena to be found in infectious mononucleosis. Forssman heterophil antibodies are probably increased prior to the development of the heterophil antibodies of this disease and possibly are essential for their appearance. The typical lymphocytes of infectious mononucleosis are frequently found in disease entities in which a positive Paul-Bunnell has not been obtained. Only when the proportion of these abnormal cells is considerable does one find an elevated heterophil titer.

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STUDIES OF THE CELL IN NORMAL AND ARTHRITIC BOVINE CARTILAGE.*†

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Two years ago the study of hypertrophic arthritis was undertaken in our laboratory. Believing that hypertrophic arthritis is the result of cartilage cell deterioration, we recognized that progress

* Supported in part by the Bryn Mawr Fund for the Investigation and Treatment of Arthritis.

† Presented before the American Orthopaedic Association, May 7, 1940, Kansas City, Missouri.

could be made only by expanding our knowledge of articular cartilage. More particularly, it was considered essential to study the action of the normal cartilage cell. Experiments were devised to this purpose.

This paper has for its purpose the analysis and interpretation of the chemical and morphologic data accumulated during our investigations. The details of our work are appearing in publications devoted to biochemistry. It is felt that such correlation as may exist between the experimental work and the clinical problems should be presented in an interpretive form.

Technique. Bovine articular cartilage was chosen as the experimental material. Fresh material was obtained from local abattoirs. The age, sex and breed of each specimen was noted and the examination of the material began within 60 minutes after slaughtering. Slices of cartilage were cut from the distal articulations of the metacarpals and metatarsals. Some of these slices were fixed, later to be embedded, cut, stained and studied histologically. The metabolism of the remaining slices were studied by the manometric technique of Warburg. Thus it was possible in each experiment to compare the biochemical determinations with the histologic findings of contiguous slices of cartilage and to correlate both results with age, sex and breed. It is of importance to record that in the older cattle degenerative changes of the articular cartilage were present. These changes were characteristic of hypertrophic arthritis.

The material studied was separated, according to age, into three groups:

I. Young—6 weeks to 6 months.
II. Adult —1 year to 7 years.
III. Old —8 years and older.

Histologic Examination. Of the histologic examinations made, but two phases will be discussed here: A, Cartilage cell counts; B, Nuclear measurements.

A. *Cell Counts.* To determine the *cellular density* of articular cartilage the number of cells per unit volume of tissue were counted. The unit of volume used was the cubic millimeter. Over 250,000 cells were counted. The cellular densities thus obtained were checked against the breed, sex, and age of the animals. No correlations were possible between cellular density and the breed or sex of the animal. A definite correlation could be made between cellular density and the age of the animal. It was found that a direct and proportionate diminution of cellular density accompanied advancing age.

TABLE 1.—AVERAGE CELLULAR DENSITY OF ARTICULAR CARTILAGE.

	Cells per c.mm.
I. Young	133,000
II. Adult	47,000
III. Old	34,000

Expressing these findings in terms of percentage by assigning 100 to the average cellular density of young animals, it was possible

to show more graphically the diminution of the number of cells per unit volume of tissue with advancing age.

I. Young—cellular density equals 100%.
II. Adult —cellular density equals 35%.
III. Old —cellular density equals 25%.

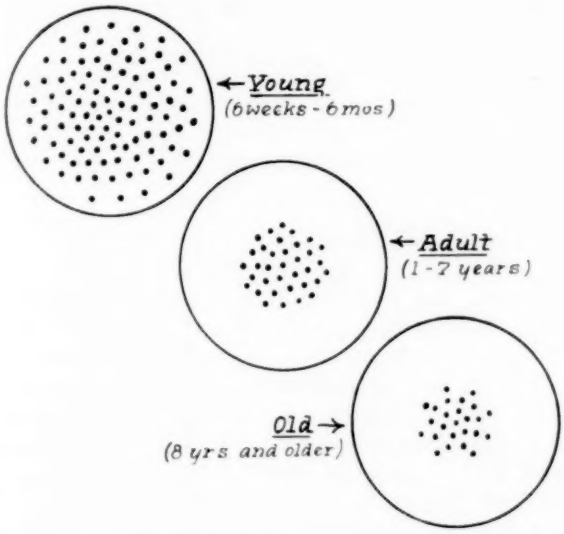

FIG. 1.—Number of cartilage cells per unit volume of tissue.

B. *Nuclear Measurements.* By projection and direct measurement the sizes of over 5000 cartilage cell nuclei were obtained. From these measurements the *volumes* of the nuclei were computed. It was found that:

1. The average nuclear volume was 90 cubic microns.
2. The average nuclear volume did not change with age.
3. Insufficient data did not warrant other conclusions although there was indication that average nuclear volume varied with the breed of cattle.

By combining the data cited in A and B, it was possible to compute that each nucleus in the young animal was surrounded by 8000 cubic microns of tissue. In other words, the relation of the nuclear volume to the volume of surrounding tissue was as 90 to 8000, or 1 to 90. This finding further illustrated the sparsity of cartilage cell distribution even in the very young animal.

Similar computations showed that in adult animals each cartilage nucleus was surrounded by 20,000 cubic microns of extranuclear tissue. In old animals the amount of tissue surrounding each nucleus amounted to 33,000 cubic microns. Hence it can be stated

that the extranuclear tissue was 250% greater in adult and 400% greater in old animals when compared to that present in young animals.

TABLE 2.—RELATION OF NUCLEAR VOLUME TO EXTRANUCLEAR TISSUE VOLUME.

I. Young	1 to 90
II. Adult	1 to 200
III. Old	1 to 370

Further analyzing the above data the internuclear distances were determined.

TABLE 3.—INTERNUCLEAR DISTANCES.

	Microns.
I. Young	20.0 (100%)
II. Adult	27.2 (136%)
III. Old	32.1 (160%)

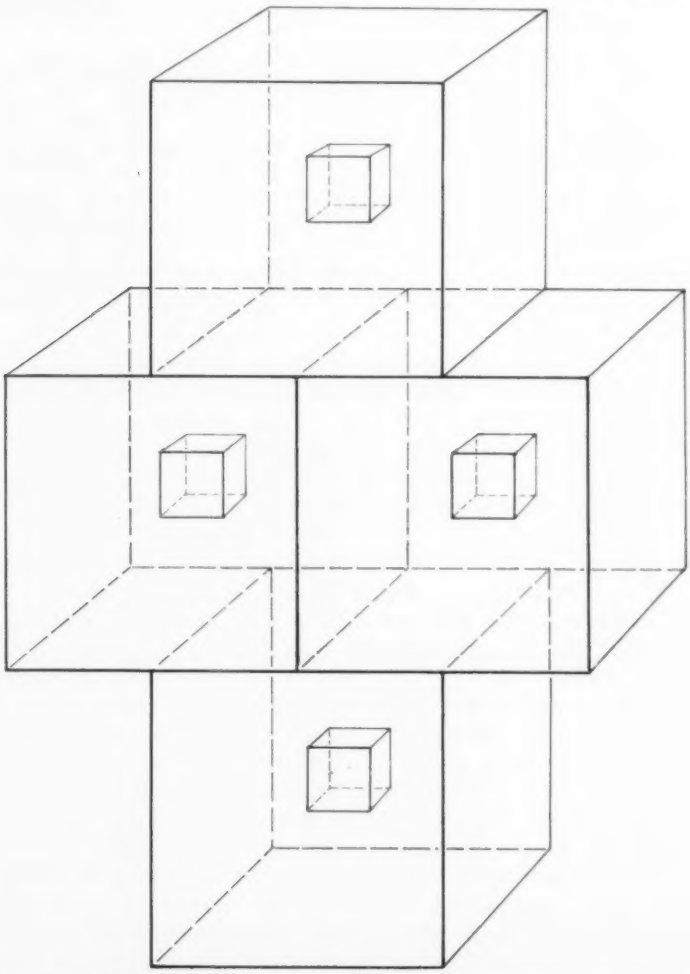

FIG. 2.—Spatial position of cartilage nuclei. (Articular cartilage of calves.)

Metabolism. The metabolism determinations made on surviving slices of bovine articular cartilage were concerned with:

A. Glucolytic Activity or Splitting of Glucose.

B. Oxidative Activity or Oxygen Consumption.

C. Dehydrogenatic Activity or Mobilization of Hydrogen.

A. *Glucolytic Activity.* The ability of articular cartilage to split glucose, as well as other hexoses under both aërobic and anaërobic conditions, was analyzed in 28 experiments. The rate of glucolysis per unit weight of cartilage decreased with progressing age of the animals. When the rate was correlated with the cellular density of the material under analysis it was found that the old cartilage cell was able to split glucose as rapidly as the young cell. In other words, there was no decline of glucolytic activity *per cell* in articular cartilage with advancing age.

Cell respiration is synonymous with oxidation or combustion. The sole function of respiration is to provide energy and hence life for the cell. Impairment of respiration means cell deterioration, and if continued, results in aging or death of the cell.

Respiratory power of a living cell depends upon the orderly action of two main units of the respiratory system:

(*a*) Dehydrogenatic System: This system mobilizes the hydrogen from various nutrients. It consists of: 1, specific enzymes which combine with the nutrients and activate their hydrogen; and of: 2, specific organic compounds and enzymes which combine with the activated hydrogen and carry it to the—

(*b*) Oxygen activating system which takes the hydrogen from the carriers and combines it with gaseous oxygen.

(The measurements of the capacities of the Oxygen Activating System are recorded under (*B*) Oxidative Activity and the capacities of the Dehydrogenatic System are recorded under (*C*) Dehydrogenatic Activity.)

B. *Oxidative Activity.* The ability and rate of articular cartilage to consume oxygen in the absence of glucose was measured quantitatively in 50 experiments. (The rate of oxygen consumption in the presence of glucose was measured in 20 experiments. The addition of glucose did not increase oxygen consumption but lowered it.)

The rate of oxygen consumption per unit weight of cartilage decreased rapidly with advancing age. In contrast to glucolysis, however, this decrease in respiration proceeded more rapidly than the diminution in cellular density.

Thus, it is seen that under comparable experimental conditions the old cartilage cell consumes less oxygen than the young cartilage cell (*cp.* Fig. 3). This suggests that the respiratory power of the old cartilage cell is diminished.

(*C*) *Dehydrogenatic Activity.* The ability of the cartilage cell to mobilize hydrogen was determined in 34 experiments by measur-

ing the oxygen uptake of cartilage slices in the presence of methylene blue. This auto-oxidizable redox dye was used as a substitute for the oxygen activating system in the cell in order to estimate the full capacity of the dehydrogenatic system. When the dehydrogenatic activity was correlated with the cellular density, it was apparent that the aging cartilage cell lost but little of its dehydrogenatic power (*cp.* Fig. 3, Hydrogen mobilization).

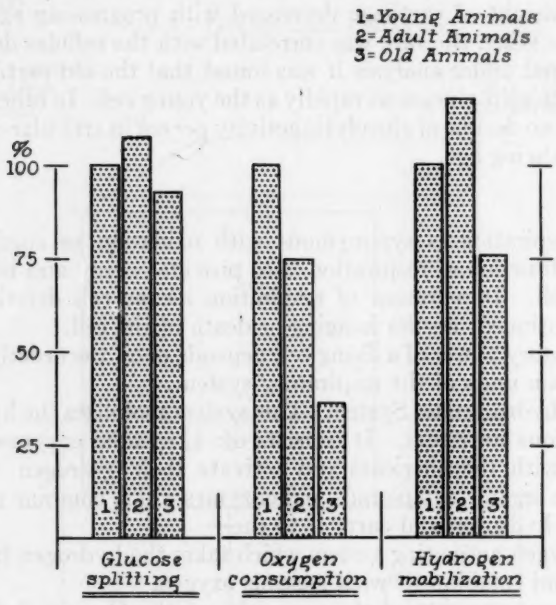

FIG. 3.—Metabolic activity of the cartilage cell.

Summarizing the experiments on respiration it can be stated that:

1. Respiration or oxygen consumption of the articular cartilage cell decreases with age.

2. The rate of respiration decreases more rapidly than can be accounted for by the diminution of the number of cartilage cells which results from aging.

3. The progressive failure of oxygen consumption with age is due to the failure of the oxygen activating system, alone of the three units responsible for cell respiration.

Conclusion and Summary. The joint surfaces of adult cattle may show degenerative changes of the articular cartilage which are typical of hypertrophic arthritis.

Histologic and metabolic studies were made of articular cartilage cells from young, adult and old cattle.

1. Articular cartilage cells diminish in number with advancing age.

2. The nuclei of cartilage cells do not decrease in volume with aging.

3. The ability of the old cartilage cell to split glucose is not less than that of the young cell.

4. The oxygen consumption activity of the old cell is much less than that of the young cell.

5. The declining respiratory rate of the old cartilage cell is due to the failure of the oxygen activating system.

6. It is suggested that the degenerative changes of articular cartilage which accompany aging are related to:

(*a*) Diminution in number of the cartilage cells incident to age.

(*b*) Inability of the old cartilage cell to "breathe" adequately.

THE INCIDENCE OF BRUCELLOSIS IN PATIENTS WITH RHEUMATIC DISEASE.

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Joint and muscle pains may be dominant features of brucellosis.[7] It is stated[1] that over 50% of patients with brucellosis have rheumatic complaints, which include arthralgia, myalgia, non-suppurative or suppurative arthritis, spondylitis, osteoperiostitis or osteomyelitis. Symptoms referable to the joints were the *chief complaint* in 10% of 67 cases of brucellosis reported by Simpson and Frazier.[11] Hardy and his coworkers[6] found an incidence of arthralgia in 32% of their cases of brucellosis, but evidence of joint inflammation occurred in less than 2%. The incidence and type of joint involvement differs with different strains of the infecting organism. In California where bovine strain of Brucella is the predominant type of organism,[12] the incidence and prominence of joint pains was greater than in Iowa where the porcine strain predominated.[7] However, the bovine strain of Brucella causes actual joint inflammation rarely, whereas the porcine strain produces arthritis more commonly but less often than the melitensis strain (Hardy). Thus, arthralgia is more common in cases caused by the bovine strain, and joint inflammation, although much less frequent than arthralgia, is usually due to the porcine or melitensis strain.

* The Rackham Arthritis Research Unit is supported by the Horace H. Rackham School of Graduate Studies, University of Michigan.

Goldfain[4a] studied the incidence of brucellosis in patients with rheumatic complaints, most of whom were from rural regions of Oklahoma where milk is rarely pasteurized. Thirty-one of 50 patients were diagnosed as having active brucellosis. The rheumatic diagnosis in these 31 cases were: atrophic arthritis, 9 cases (29%); hypertrophic arthritis, 5; ankylosing spondylitis, 1; chronic fibrositis, 5; psychoneurosis and chronic fibrositis, 2; sciatica, 2. Psychoneurosis alone occurred in 5 cases. The diagnosis of brucellosis was based entirely on laboratory procedures (the skin test, phagocytic index and agglutination reaction) performed and interpreted according to the criteria of Keller, Pharris and Gaub[10] as adapted from Huddleson, Johnson and Hamann[9] (Table 1).

TABLE 1.—SYSTEM PROPOSED BY HUDDLESON FOR THE DIAGNOSIS OF BRUCELLOSIS.

Agglutination test.	Skin test.	Phagocytic power of blood.	Status of patient toward Brucella.
Negative	Negative	0 to 20% of cells, slight	Susceptible
Negative	Positive	0 to 40% of cells, marked	Infected
Positive	Positive	0 to 40% of cells, marked	Infected
Negative	Positive	60 to 100% of cells, marked	Immune
Positive	Positive	60 to 100% of cells, marked	Immune

Later, Goldfain[4b] reported that, by the same criteria, of 157 patients with rheumatic, neuralgic and/or arthritic symptoms, 80 (51%) had active brucellosis. Twenty-three of these were re-tested after completion of a full course of bacterine therapy and again 3 months later. In the majority of these the skin test became negative or less positive, the leukocytes showed increased phagocytic power and blood agglutinins increased. Twenty-one of the 23 patients became free of symptoms or were improved. It was concluded that recognition and treatment of brucellosis in patients with rheumatic disease favorably influences the course of the rheumatism even though this may not be directly caused by the brucellosis.

These reports of Goldfain suggest that brucellosis is much more frequent in patients with rheumatic disease than is generally considered to be the case. We wondered whether his statistics accurately indicated the prevalence of brucellosis generally throughout this country or whether the high incidence of brucellosis in rheumatic patients might be peculiar to a region in which this disease is rampant. To obtain information regarding the incidence and importance of active brucellosis in patients with rheumatoid arthritis and other types of rheumatic diseases in Michigan the following study was conducted.

Method. Fifty patients who came to the University Hospital with illness characterized by rheumatic symptoms were studied. These were equally divided into two distinctly different groups. The first group consisted of

25 patients with typical atrophic (rheumatoid) arthritis, so diagnosed after careful clinical, laboratory and roentgenographic study. All but 3 in this group had manifestations of activity of the disease. The second group comprised 25 patients with symptoms and manifestations which were not characteristic of any of the common arthritides. Many of these complained of arthralgia or myalgia but demonstrated no joint abnormalities clinically or roentgenographically; others reported that they had had acute joint inflammation which subsided, leaving only arthralgia; still others had hydrarthrosis, or chronic inflammatory joint disease that could not be readily classified; the remainder had periarticular disease (so-called "fibrositis" or "non-articular rheumatism"). The patients in this second group were thoroughly studied—roentgenograms of joints and sedimentation indices were routinely obtained, and when indicated the following studies were performed: systemic roentgenograms, blood cultures, gonococcal complement fixation reactions, electrocardiograms, cytologic examinations and culture of joint fluid, biopsies of muscle and periarticular tissue, sensitization tests and therapeutic tests with salicylates, colchicine, and sulfanilamide or related drugs.

The existence of brucellosis was carefully investigated by both clinical and laboratory means. The anamnesis included inquiry as to the residence, the occurrence of previous unexplained febrile illness or of brucellosis or Bang's disease in the vicinity, the use of raw milk, the raising of cattle, the occurrence of abortion among the cattle, the testing of the cattle for Bang's disease. To allow accurate interpretation of laboratory tests we inquired regarding previous skin tests or vaccine therapy for brucellosis.

The laboratory tests performed were the skin test, agglutination reaction and opsonocytophagic index against Brucella and blood culture.[2,5,8–10] Brucellergin of 1 to 1000 dilution was employed for the skin test and the reaction was observed 48 hours after injection. Adopting the criteria of Huddleson, it was considered positive if in addition to an area of erythema there was induration which measured 0.5 cm. or more in diameter. The phagocytic index and rapid slide agglutination tests were performed according to the technique of Gould and Huddleson who consider that by this method a positive test consists of complete agglutination in a titer exceeding 1 to 25. Blood for the serologic tests was obtained prior to the performance of the skin test. In attempts to culture Brucella, blood was inoculated into a phosphate buffered beef infusion broth and incubated at 37° C. in an atmosphere of 10% carbon dioxide for 16 days. At 4-day intervals plates of rabbit blood agar were inoculated from the original broth; these were also incubated in a carbon dioxide atmosphere and examined for growth after 24 and 48 hours.

Results. In none of the 25 patients with typical atrophic arthritis were positive results to all three of the diagnostic tests for brucellosis found (Table 2). In 7 cases the phagocytic index was weakly positive but in none of these was there a positive skin reaction. The skin test was positive in 2 patients as the only positive finding. Blood agglutinins for Brucella were not obtained in any of the patients in this group. Blood cultures for Brucella were performed in 12 cases; all were negative.

Table 3 contains the results in the 25 patients with findings that were not typical of any of the common arthritides. Three of this group had significant blood agglutinins and in addition a positive skin test and positive phagocytic index for Brucella. The combination of positive skin test and phagocytic index occurred in 1 instance

and the combination of a positive skin test and positive agglutination test occurred in another. In 4 cases a skin reaction was the only positive laboratory finding. Blood cultures for Brucella, performed in 23 cases, were negative.

TABLE 2.—RESULTS OF STUDIES ON PATIENTS WITH TYPICAL ATROPHIC ARTHRITIS.

Case.	Residence.	Raised cattle.	Cattle tested for Bang's disease.	Occurrence of abortions among cattle.	Used raw milk.	Previous skin tests or vaccine therapy in patients.	Activity of arthritis.	Brucella agglutination test.	Brucellergin skin test.	Phagocytic index for Brucella.	Blood culture for Brucella.
1	Rural	Yes	No	No	Yes	None	Inactive	Neg.	Neg.	Neg.	Neg.
2	Rural	Yes	?	?	Yes	Both	Active	Neg.	Neg.	Neg.	Neg.
3	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
4	Rural	Yes	No	Yes	Yes	None	Active	Neg.	Neg.	Neg.	Neg.
5	Urban	No	..	..	No	None	Active	Neg.	Neg.	50% None 46% Slight 4% Moderate	Neg.
6	Urban	No	..	..	No	None	Active	Neg.	Neg.	24% None 64% Slight 12% Marked	Neg.
7	Rural	Yes	Yes	No	Yes	None	Active	Neg.	Neg.	16% None 74% Slight 10% Moderate	Neg.
8	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	12% None 70% Slight 18% Moderate	Neg.
9	Rural	Yes	Yes	No	Yes	None	Inactive	Neg.	Neg.	Neg.	
10	Urban	No	Yes	No	Yes	None	Active	Neg.	Neg.	Neg.	
11	Urban	No	..	..	No	None	Active	Neg.	Neg.	Neg.	
12	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	
13	Urban	No	..	..	No	None	Active	Neg.	Neg.	90% None 10% Slight	Neg.
14	Urban	Yes	?	?	Yes	None	Active	Neg.	Neg.	96% None 4% Slight	Neg.
15	Rural	Yes	Yes	No	Yes	None	Inactive	Neg.	Pos.	Neg.	
16	Urban	No	Yes	No	Yes	None	Active	Neg.	Neg.	Neg.	
17	Urban	No	..	..	No	None	Active	Neg.	Neg.	Neg.	
18	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	
19	Urban	No	..	..	No	None	Active	Neg.	Neg.	Neg.	
20	Rural	Yes	Yes	No	Yes	None	Active	Neg.	Neg.	Neg.	
21	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	
22	Rural	Yes	Yes	No	Yes	None	Active	Neg.	Pos.	Neg.	Neg.
23	Urban	No	..	..	No	None	Active	Neg.	Neg.	Neg.	
24	Rural	Yes	No	No	Yes	None	Active	Neg.	Neg.	Neg.	
25	Urban	No	..	..	No	None	Active	Neg.	Neg.	76% None 20% Slight 4% Moderate	Neg.

Discussion. To obtain precise data as to incidence of a disease it is necessary to have indisputable diagnostic tests. Unless the organisms are isolated, the existence of brucellosis cannot be proven. It is generally agreed that the laboratory tests for brucellosis are often confusing, may even be misleading and allow for different interpretation. The agglutination test is the most reliable of the common diagnostic procedures, but it is not infallible. Evans[5] found a negative agglutination test (titer less than 1 to 40 by the tube method) in 46% of patients with chronic brucellosis. Other authors report absence of agglutinins in 5% to 15% of the cases. Opinions differ as to the minimum titer that is diagnostically significant. Furthermore, there are sources of possible error in inter-

pretation because the titer may remain high after recovery from the disease or agglutinins may develop in individuals exposed to infection although they have never been ill.

The brucellergin skin test is less reliable than the agglutination test because it is less specific. In Evans' series a positive skin test occurred only four times as frequently in patients with chronic brucellosis as in patients ill with other diseases. Three explanations have been advanced for the occurrence of a positive skin test in the absence of active brucellosis. Repeated contacts with Brucella incident to handling infected animals or drinking infected milk may produce a state of hypersensitiveness as manifested by skin reaction to Brucella antigens although symptoms of disease have never been present. Secondly, the allergic state may persist for years after complete recovery from the disease. Thirdly, "false positive" brucellergin tests do occur, possibly on the basis of general bacterial hypersensitivity. Evans and her associates found a positive skin test in 13.7% of 321 patients ill with diseases other than brucellosis and in 10.7% of healthy subjects.

The phagocytic index is the least reliable of the diagnostic test because it is the least specific. This test was found by Evans to be positive in 30.7% of patients ill with chronic diseases other than brucellosis. Huddleson, Keller and others believe that the degree of the phagocytic activity indicates the patient's status in regard to the infection (susceptible, actively diseased or immune). Evans and her associates do not agree inasmuch as they found no consistent correlation between the phagocytic power of the leukocytes and the state of the infection. Our experience with this test is in accord with Evans. Positive phagocytic and skin tests add weight to the evidence given by a positive agglutination reaction. In Evans' series the combination of all three positive reactions occurred ten times as frequently in chronic brucellosis as in patients ill with other diseases. However, brucellosis, proved by recovery of the organism, may occur even though all three tests give negative results.[3]

Since recovery of Brucella by culture or by animal inoculation can be accomplished in only a small percentage of the cases, requiring this for establishment of the diagnosis would result in not diagnosing the disease in many instances. In our cases no positive blood cultures were obtained so that the diagnosis of brucellosis is not unequivocal. We considered the disease to exist when the history, clinical findings, specific laboratory tests for brucellosis and the exclusion of other disease indicated that chronic brucellosis was the most likely diagnosis. The diagnosis of *possible* chronic brucellosis was made if the above-mentioned evidence was less convincing.

We feel that brucellosis did not exist in any of the patients with typical atrophic arthritis (Group 1). In none were the history, symptomatology and physical findings suggestive of, or the

TABLE 3.—RESULTS OF STUDIES ON PATIENTS WITH RHEUMATIC SYMPTOMS AND MANIFESTATIONS NOT CHARACTERISTIC OF ANY OF THE COMMON ARTHRITIDES.

Case.	Residence.	Raised cattle.	Cattle tested for Bang's disease.	Occurrence of abortions among cattle.	Used raw milk.	Previous skin tests or vaccine therapy in patients.	Fever.	Rheumatic symptoms.	Physical signs of joint disease.	Brucella agglutination test.	Brucellergin skin test.	Phagocytic index for Brucella.	Blood culture for Brucella.	Final diagnosis.
1	Urban	No	..	..	No	None	Yes	Transient red, swollen joints; muscle soreness	Transient acute joint inflammation; muscle tenderness	Neg.	Neg.	Neg.	Neg.	Angiodermatomyositis; acute lupus erythematosus disseminatus
2	Rural	Yes	Yes	No	Yes	None	No	Swelling of left knee every 9 days	Hydrarthrosis without bony abnormality	(2) Neg.	..	76% None 24% Slight	Neg.	Intermittent hydrarthrosis, ovalbumin sensitivity
3	Urban	No	..	..	No	None	No	Aches in neck, shoulders, arms and legs	None	Neg.	Pos.	14% Moderate 86% Marked	Neg.	Psychoneurosis
4	Rural	Yes	No	No	Yes	None	Yes	Arthralgia and myalgia, legs and knees	None	Pos. 1:100	Pos.	2% None 2% Slight 6% Moderate 90% Marked	..	Chronic brucellosis
5	Urban	No	No	Yes	Yes	None	Yes	Arthralgia and myalgia, legs and arms	None	Pos. 1:80	Pos.	Neg.	Neg.	Possible chronic brucellosis
6	Rural	Yes	No	Yes	Yes	None	Yes	Arthralgia, knees and ankles	None	Pos. 1:50	Pos.	22% None 15% Slight 17% Moderate 46% Marked	Neg.	Chronic brucellosis
7	Urban	No	..	..	No	None	Yes	Painful, stiff shoulders, knees and wrists	Hydrarthrosis both knees; limitation in motion both wrists	Neg.	Neg.	Neg.	Neg.	Atypical atrophic arthritis
8	Rural	Yes	?	?	Yes	None	Yes	Painful, swollen right knee and heels	Acute joint inflammation, right knee; Achilles' bursitis	Neg.	Neg.	Neg.	Neg.	Gonococcal arthritis and bursitis
9	Urban	Yes	Yes	No	Yes	None	No	Severe arthralgia of elbows, knees and shoulders	None	Pos. 1:200	Pos.	100% Marked	Neg.	Chronic brucellosis
10	Rural	Yes	Yes	No	Yes	None	Yes	Arthralgia, both knees	None	Neg.	Pos.	Neg.	Neg.	Possible chronic brucellosis
11	Rural	Yes	No	Yes	Yes	None	Yes	Arthralgia and myalgia, both arms	None	Neg.	Pos.	Neg.	(2) Neg.	Possible chronic brucellosis

11	Rural	Yes	No	Yes	Yes	None	Yes	Arthralgia and myalgia, both arms	None					
12	Rural	Yes	No	No	Yes	None	Yes	Pain and stiffness of fingers and shoulders	Limitation of motion of shoulders and finger joints with puckering of the subcutaneous tissue of the palms	Neg.	Neg.	Neg.	Neg.	Fibrositis
13	Urban	No	..	..	No	None	Yes	Painful swelling of all joints	Acute inflammatory changes of the joints	Neg.	Neg.	....	Neg.	Felty's syndrome with superimposed hemolytic streptococcus septicemia
14	Rural	Yes	Yes	No	Yes	None	No	Painful, stiff shoulders and fingers	Periarthritis of shoulders; tenderness and swelling of metacarpophalangeal joints and proximal phalangeal joints	Neg.	Neg.	Neg.	Neg.	Periarthritis of shoulders; atrophic arthritis of hands
15	Urban	No	..	..	No	None	Yes	Myalgia of lower extremities, shoulders and forearms	Muscle tenderness	Neg.	Neg.	Neg.	(2) Neg.	?Muscular rheumatism
16	Urban	No	..	..	No	None	Yes	Low back pain; arthralgia of shoulders, neck, feet, left knee and wrist	Fusiform swelling and stiffness of proximal phalangeal joints of right index finger	Neg.	Neg.	Neg.	Neg.	Atrophic arthritis
17	Rural	Yes	No	No	Yes	None	Yes	Severe arthralgia shoulders, hands and knees	None	(3) Neg	Neg.	(3) Neg.	(2) Neg.	Undiagnosed
18	Rural	Yes	No	Yes	Yes	None	Yes	Swollen wrists; soreness of shoulders, neck, hip, knees and feet	Acute inflammatory changes of both wrists and all metatarsophalangeal joints	Neg.	Neg.	Neg.	Neg.	Atypical atrophic arthritis
19	Urban	No	..	..	No	None	Yes	Swelling of right knee	Hydrarthrosis	Neg.	Neg.	Neg.	Neg.	Hydrarthrosis, ?etiology
20	Rural	Yes	No	No	Yes	None	Yes	Arthralgia, arms and shoulders; pain and swelling of both ankles	Pes planus	Neg.	Pos.	Neg.	Neg.	Possible chronic brucellosis
21	Rural	Yes	Yes	No	Yes	None	Yes	Arthralgia, elbows and knees	None	Neg.	Neg.	Neg.	Neg.	?Rheumatic fever
22	Urban	No	..	..	No	None	Yes	Swelling of knees, ankles, shoulders, wrists and elbows	Hydrarthrosis, both knees	Neg.	Neg.	7% None 30% Slight 63% Moderate	Neg.	Atypical atrophic arthritis
23	Rural	Yes	No	Yes	Yes	None	Yes	Arthralgia and myalgia, arms and legs	None	Neg.	Neg.	Neg.	Neg.	?Psychoneurosis; possible chronic brucellosis
24	Urban	No	..	..	No	None	Yes	Painful swelling of knees, ankles, wrists and elbows	None	Neg.	Neg.	Neg.	Neg.	?Malingering
25	Rural	Yes	No	No	Yes	None	Yes	Arthralgia and myalgia of legs	None	Neg.	Pos.	Neg.	Neg.	Possible chronic brucellosis

laboratory studies diagnostic of, brucellosis. The finding of phagocytic power toward Brucella in 28% of this group was to be expected since Evans found a positive phagocytic reaction in 30.7% of patients with chronic diseases other than brucellosis. In the absence of other evidence for brucellosis, we interpret a positive phagocytic test as a "false positive" and not diagnostic of active brucellosis. The two skin reactions occurred in farmers who had cattle on their farms and who used raw milk. The history, physical examination and other laboratory tests failed to yield further evidence for active brucellosis. Since Evans found a positive skin test in 13.7% of patients ill with diseases other than brucellosis and in 10.7% of healthy subjects, the occurrence of two skin reactions in our 25 cases (8%) is not surprising.

In our second group of patients the diagnosis of chronic brucellosis was made in 3 instances and "possible chronic brucellosis" was diagnosed in 6 cases. All 3 of the patients diagnosed as chronic brucellosis had drunk unpasteurized milk. Two had low-grade fever, one (Case 9) was afebrile. All gave positive results to the three diagnostic tests. In 2 (Cases 4 and 9) the leukocytes showed marked phagocytic activity to the extent that according to Huddleson's criteria they would have been classified as "cured." Yet, they exhibited manifestations of active disease. All complained of *arthralgia* but exhibited no joint abnormalities. One (Case 6) stated that at the onset of his illness his knees and ankles were swollen and red; these changes disappeared and he had only arthralgia when he entered the hospital. Case 4 was treated with repeated courses of sulfanilamide therapy without any appreciable benefit. Case 6 was given sulfanilamide and Brucellin vaccine (Parke-Davis) and was afebrile and free of symptoms when discharged. Case 9 was treated with sulfanilamide and during this therapy fever was produced by intravenous injection of typhoid antigen three times. There was marked improvement. He had been bed-ridden because of severe arthralgia; at the time of discharge he was ambulatory, and complained of only minimal aching in the right shoulder and elbow.

In the group of 6 patients with "possible chronic brucellosis" a definite diagnosis would have been made in at least 3 instances if less rigid criteria were employed. Case 5 used raw milk from infected cows and had positive agglutination and skin tests for Brucella. She also had non-specific bronchitis. Whether brucellosis or bronchitis accounted for her symptoms is not clear. The positive laboratory tests could have been due to brucellosis in the past. Sulfapyridine therapy resulted in a complete cure. Case 11 was diagnosed brucellosis 6 years before we saw him because a positive agglutination test was found after he drank raw milk. During our study a skin reaction was the only positive test. He was given sulfanilamide without any effect. Case 20 complained of mild

arthralgia of the joints of the upper extremities, painful, swollen feet and low-grade fever. He had consumed raw milk. He had pes planus and foot strain which could have accounted for his foot complaints; other symptoms were minimal and no treatment for brucellosis was administered. Positive skin tests were observed in Case 10 who had a duodenal ulcer and Case 25 who had pernicious anemia in remission. Their joint difficulties and occasional mild temperature elevations were considered insufficient to warrant treatment for possible brucellosis. Case 23 complained of asthenia, constipation, arthralgia and myalgia of the extremities, and had low-grade fever. He used raw milk and abortion had occurred among his cows. All the tests for brucellosis yielded negative results.

Thus, by our criteria, none of the 25 patients with characteristic atrophic arthritis had active brucellosis. Of the 25 patients in Group 2, those with miscellaneous rheumatic disorders, 3 (12%) were diagnosed active brucellosis and 6 (24%) were diagnosed as "possible brucellosis"—a total of 36% of a group who might have had undulant fever. Of all 50 cases (Groups 1 and 2), the incidence of brucellosis was 18% (including the 6 cases with "possible brucellosis").

To satisfactorily contrast our findings with the reports of Goldfain, it is necessary to analyze our cases by the criteria he used which depend entirely on the laboratory tests (Table 1). By these criteria 2 of our patients with atrophic arthritis would be diagnosed as active brucellosis, an incidence of 8%. This incidence is far less than 46% which occurred in Goldfain's cases of atrophic arthritis. Six cases (24%) of our Group 2 would by his method be diagnosed as active brucellosis. Thus, a total of 8 cases (16%) of our 50 patients had brucellosis by the criteria of Goldfain, in contrast to 62% of 50 patients reported by him! Many of our patients were farmers and used unpasteurized milk, comparable in these respects to the patients studied by Goldfain. These findings show quite clearly that the incidence of brucellosis in patients coming to the hospital complaining primarily of rheumatic symptoms is decidedly less in Michigan than in Oklahoma, most likely because the prevalence of this disease is less in Michigan than in Oklahoma.

Thus, the importance of brucellosis in regard to rheumatic disorders is far less in Michigan and probably most parts of the United States than the reports of Goldfain suggest. Arthralgia and other rheumatic *symptoms* are, to be sure, frequently observed in brucellosis, and that disease should be suspected especially in febrile patients with rheumatic complaints. However, joint inflammation was not observed in any of our patients who had brucellosis, or even "possible brucellosis." It seems quite clear, therefore, that brucellosis is seldom, if ever, the cause of chronic non-suppurative polyarthritis.

Conclusions. The incidence of brucellosis was studied in 25 patients with characteristic atrophic arthritis and in 25 cases of other

rheumatic disorders. None of the first group had evidence which, by our criteria, was diagnostic of brucellosis. Of the second group, 3 (12%) had quite convincing evidence of active brucellosis, and 6 others had "possible brucellosis." The incidence of brucellosis in rheumatic patients is, therefore, much less in Michigan and probably most parts of the United States than is reported from Oklahoma.

Arthralgia and other rheumatic symptoms are common in brucellosis and *temporary*, non-purulent joint inflammation may occur. Our data indicate that brucellosis is seldom, if ever, a cause of *chronic* non-purulent joint inflammation.

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INCIDENCE OF PULMONARY TUBERCULOSIS IN SCHIZOPHRENIC PATIENTS FOLLOWING METRAZOL CONVULSIVE THERAPY.

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The treatment of functional psychoses with metrazol convulsive therapy is used extensively in many hospitals. Although numerous reports have been published dealing with dangers of this treatment, such as vertebral fractures and lung abscesses, comparatively little emphasis has been laid upon a possible complication in the form of pulmonary tuberculosis. That schizophrenic patients, who have been in institutions for many years, develop tuberculous lesions is not a new observation. However, the incidence of tuberculosis appeared to be much higher in our patients after treatment with metrazol. This was especially noted in our autopsy material, since in 6 out of 7 patients a severe tuberculous involvement of the lungs was observed.

Already von Meduna and Friedman[3,5] have mentioned 1 patient who died of acute pulmonary tuberculosis following metrazol treatment. Kraus[2] reported 1 patient out of 64 cases treated with metrazol, who did not present Roentgen ray findings 9 months previous to the treatment, but developed an acute tuberculous pneumonia after 6 injections of metrazol. van de Graaff[6] *et al.* also reported 4 cases of tuberculous pneumonia following treatment. They considered the possibility that cardiazol injections might have activated a latent pulmonary tuberculosis. Demay[1] *et al.* reported 3 cases of schizophrenia with manifestations of pulmonary tuberculosis after metrazol therapy. Recently, in a comprehensive survey of the consequences of metrazol, Read[4] stressed the occurrence of pulmonary tuberculosis following metrazol treatment.

To obtain more objective data on the relationship between metrazol therapy and the incidence of tuberculosis, all coöperative schizophrenic patients (277 in all) who had been previously treated with metrazol, as well as a comparable non-treated group, were carefully reëxamined. These examinations consisted of a careful physical examination and fluoroscopic studies. In those with doubtful findings, Roentgen ray films were taken. In this way 25 schizophrenic patients (18 men and 7 women) were found to have tuberculous lesions which had developed either during or following the course of metrazol treatment. None of these patients presented clinical signs of pulmonary tuberculosis before the therapy was instituted, though the amount of latent tuberculosis present could not be estimated from the evidence available. Most of them had been in the hospital for some time, and in only 1 patient was the hospitalization period of short duration (4 months). The average period of hospitalization was 47 months prior to metrazol treatment. The percentage of active cases of tuberculosis was 8.3 in the group treated with metrazol over a period of 3 years, which is considerably higher than that of tuberculosis in the rest of our schizophrenic patients (3%) during the same period of 3 years. The higher percentage is even more significant since patients who were considered poor risks were rarely treated with metrazol.

Most of the patients who developed tuberculosis were in the age group of 20 to 29 years (Table 1). However, it is striking that those who developed tuberculosis *immediately* following metrazol treatment were considerably older than the rest of the group. Four were over 40 and 2 over 30 years of age. Thus, it seems that the pulmonary status of patients over 40 should be carefully studied before institution of this therapy.

The amount of metrazol and the number of convulsions present no direct relationship to the development of tuberculosis or the severity of the lesion (Table 1).

The onset of the tuberculous process in many of these patients was not only acute, but also dramatic. In some patients the infec-

tion was so overwhelming as to simulate clinically a picture of lobar pneumonia with high temperature, respiratory distress and local physical findings. In 2, the tuberculous process started with a pleurisy with effusion. In 3, the metrazol treatment had to be interrupted because of development of pulmonary tuberculosis, while in the remainder a varying period of time intervened before the tuberculous process was discovered. It is very difficult to detect clinically small and even large tuberculous lesions in uncooperative psychotic patients. Although all our chronic patients have a complete physical examination at 6-month intervals, 5 patients who had no clinical findings of tuberculosis when this study was started and who had not been suspected, were discovered on the fluoroscopic survey to have *early* pulmonary tuberculosis (see Table 1). This finding emphasizes the importance of routine pulmonary fluoroscopy in a mental hospital, especially for those patients who receive convulsive therapy.

The course of the tuberculous process in many of our patients was acute and progressive; 9 died, 4 of them within 4 months after the first appearance of the infection. Five illustrative case histories follow, indicating the course of events in several of those patients with acute onset. Tubercle bacilli were demonstrated in the sputum or by guinea-pig inoculation in all patients.

Case Abstracts. Case 1.—E. D., female, 43 years of age, admitted October 19, 1928, diagnosed hebephrenic dementia precox. Mental symptoms began in 1925, at the age of 30 with untidiness in habits and levelling of emotion. On admission she was extremely indifferent, out of contact, and actively hallucinated. For the past 10 years, her mental condition has been stationary. Metrazol therapy started on August 29, 1938. Three weeks later, the day after her ninth convulsion, she became acutely ill, developed a temperature of 104°, and dullness over the entire left lung with occasional crepitant râles. Temperature dropped the next morning to 100.2°. Roentgen ray taken a few days later revealed a large cavity below the fourth rib anteriorly in the left lung with soft exudative infiltration about it. The patient continued to have a septic fever with progressive tuberculosis and expired on October 8, 1938.

Case 2.—B. L., female, 33 years of age, admitted December 15, 1933, diagnosed catatonic dementia precox. She had been ill for many years, was manneristic, impulsive, had bizarre ideas, and attitudinized. Here, she actively hallucinated, attitudinized and was impulsive. Started on metrazol therapy on January 10, 1938, receiving 20 treatments with 15 convulsions with marked mental improvement. On March 25, 1938, she relapsed mentally and received 3 more treatments. The day after the last convulsion she became acutely ill with a temperature of 104.6°. Roentgen ray revealed left pleurisy with effusion. Patient was treated on the tuberculosis service until July 31, 1939, when she was discharged arrested.

Case 3.—E. R., male, 23 years of age, admitted July 24, 1936, diagnosed undetermined dementia precox. Five weeks before admission a change of personality was noted, when he became depressed and began to act peculiarly. Roentgen ray taken July 27, 1936, was negative for pulmonary tuberculosis. He became a feeding problem and on December 6, 1937, was started on metrazol therapy, receiving nine shocks. On December 29, 1937, 2 days after his last convulsion, he became acutely ill with a tempera-

ture of 105° and physical findings suggestive of tuberculous pneumonia. Roentgen ray on January 3, 1938 (4 days later) showed a marked area of infiltration 8 cm. in diameter in the middle zones of the right lung On March 15, 1938, a right tuberculous pleurisy with effusion developed. The patient was paroled improved on June 12, 1938, with active tuberculosis, and transferred to a tuberculosis sanitarium.

CASE 4.—E. N., male, 23 years of age, admitted April 3, 1936, diagnosed hebephrenic dementia precox. There was a gradual onset of the psychosis with bizarre ideas and untidy habits. On May 27, 1937, he was started on metrazol therapy and received 23 convulsive treatments. On August 31, 1937, 4 days after the last convulsion, a tuberculous pleurisy with effusion developed. Patient remained on the tuberculous service until his death on November 20, 1939, from progressive pulmonary tuberculosis.

CASE 5.—L. T., female, 43 years of age, admitted October 16, 1937, diagnosed hebephrenic dementia precox. She had been mentally ill since 1927, with carelessness about her personal appearance, uncoöperativeness, hallucinations, and impulsive behavior. On February 3, 1938, metrazol therapy was started. On April 12, 1938, 12 days after her seventeenth convulsion, a pneumonic process developed in the right upper lobe with a temperature of 103°. Roentgen ray showed moderately advanced tuberculosis. Her pulmonary condition did not improve with bed rest, and on August 9, 1938, she was started on artificial pneumothorax. On August 11, 1939, she was discharged from the tuberculous service as an arrested case with mental condition unchanged.

TABLE 1.—PULMONARY TUBERCULOSIS AFTER METRAZOL CONVULSIONS

Patient.	Sex.	Age.	Metrazol.		Pulmonary tuberculosis.			
			Convulsion.	Grams.	Occurrence after last convulsion.	Type of onset.	Degree of involvement on Roentgen ray.	Course.
1 E. D.	F	42	9	4.4	1 day	Acute	Far advanced	Death
2 B. L.	F	33	17	13.8	1 "	Acute	Pleural eff.	Arrested
3 E. R.	M	23	9	8.7	2 days	Acute	Mod. adv.	Arrested
4 E. N.	M	23	23	18.4	4 "	Acute	Far adv.	Death
5 L. T.	F	43	16	8.8	12 "	Acute	Mod. adv.	Arrested
6 W. L.	M	40	29	28.8	14 "	Acute	Mod. adv.	Death
7 H. J.	M	30	15	8.7	24 "	Acute	Pleural eff.	Arrested
8 L. R.	M	26	25	16.3	49 "	Fluoro.	Minimal	Arrested
9 E. G.	F	41	10	4.0	16 wks.	Acute	Far adv.	Death
10 A. D.	F	26	28	13.6	5 mos.	Chronic	Far adv.	Death
11 O. Q.	M	18	50	45.8	8 "	Chronic	Far adv.	Death
12 O. H.	M	24	15–	10.6	9 "	Fluoro.	Minimal	Active
13 M. K.	F	32	15	9.4	10 "	Chronic	Mod. adv.	Active
14 H. F.	M	21	26	24.3	11 "	Chronic	Minimal	Arrested
15 E. S.	M	34	2	1.5	12 "	Chronic	Mod. adv.	Active
16 S. R.	F	25	10	6.4	13 "	Chronic	Minimal	Arrested
17 J. E.	M	27	25	17.9	14 "	Chronic	Minimal	Active
18 E. T.	M	29	15	12.0	15 "	Chronic	Minimal	Active
19 W. G.	M	18	25	24.9	16 "	Chronic	Mod. adv.	Death
20 J. K.	M	37	43	50.3	16 "	Chronic	Far adv.	Death
21 A. T.	M	26	11	8.2	17 "	Chronic	Far adv.	Death
22 W. A.	M	39	60	49.8	18 "	Chronic	Mod. adv.	Arrested
23 F. R.	M	24	25	16.0	22 "	Fluoro.	Minimal	Arrested
24 J. P.	M	45	42	23.0	25 "	Fluoro.	Minimal	Active
25 A. F.	M	27	25	18.0	25 "	Fluoro.	Minimal	Active

Comment. The data presented in Table 1 show that metrazol convulsive therapy has caused a considerable increase in the incidence of pulmonary tuberculosis in the Elgin State Hospital. This increase is even more pronounced if one considers the fact that the patients treated with metrazol were carefully selected, and those

having known tuberculosis were rejected. Whether the activation of the latent tuberculous process is due to mechanical factors causing a rupture of a walled-off focus, or whether allergic, circulatory, or toxic changes occur in the lung, can only be decided experimentally. As was observed from our material, the pulmonary lesion is usually an extensive exudative infiltration of pneumonic consolidation, often bilateral, which shows a marked tendency to progress unfavorably. Pleurisy with effusion occurs very early following treatment, but in our 2 cases was easily arrested. The importance of carefully reëxamining metrazol treated patients for pulmonary tuberculosis whether or not respiratory tract symptoms develop or an elevation in temperature occurs cannot be emphasized too strongly.

In psychiatric practice the question may arise whether one should treat the psychotic behavior even in the presence of active pulmonary tuberculosis. A very excited patient who refuses to eat and who regurgitates tube feedings and is rapidly failing physically may be in great danger if treated conservatively. Often in this type of patient metrazol will produce a rapid interruption of the psychotic picture. One of our patients was treated under such circumstances. She was rapidly failing physically, had active pulmonary tuberculosis, was resistive and uncoöperative, and regurgitated her tube feedings. However, her psychotic symptoms were of recent onset, her prepsychotic personality was good, and a careful evaluation of the psychosis pointed to a very good prognosis providing she did not die of her pulmonary tuberculosis. Accordingly, she received metrazol therapy with complete mental recovery. Her tuberculosis showed steady improvement throughout the period of treatment and later became completely arrested.

Conclusions. 1. Twenty-five (8.3%) patients with schizophrenia treated with metrazol convulsive therapy, developed pulmonary tuberculosis as compared with 3% of the schizophrenics not so treated.

2. In 9 of these the onset was acute, occurring during treatment or within 4 months of the institution of metrazol therapy. We believe most of these to be due directly to the metrazol therapy.

3. Metrazol should be given in the presence of active pulmonary tuberculosis only when all the risks have been considered and when the mental condition is very seriously influencing the physical status of the individual.

4. Careful pulmonary examination including Roentgen ray or fluoroscopic study is indicated before the institution of therapy.

5. All patients should be fluoroscoped at 3-month intervals following therapy for at least 2 years.

We wish to thank Dr. Charles F. Read, Managing Officer, for his helpful suggestions and encouragement in the completion of this study.

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A NEW METHOD FOR STUDY OF THE FASTING INSULIN REQUIREMENT OF THE SEVERE DIABETIC.

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Control of the severe diabetic continues as a major problem in insulin therapy, and plans or methods by which such patients may be successfully managed are definitely needed. Much of the difficulty in the management of these patients depends upon the fact that they require insulin not only to cover their dietary intake, but also in the period during which food is not being absorbed. This postabsorptive period occurs principally at night, with the usual dietary schedule. The amount of insulin necessary to prevent this rise of the blood sugar in the postabsorptive state is defined as the basal insulin requirement.[2a] Both of these insulin needs must be met to control the severe diabetic satisfactorily. Actual studies[4,5] indicate that two different types of insulin are required: one with a quick, strong action, suitable for covering carbohydrate absorption from the diet, properties of regular insulin, and the other with a slow prolonged action and ability to influence carbohydrate metabolism slowly, suitable for controlling the basal requirement during the night, without danger of hypoglycemia, properties of protamine zinc insulin.

A practical plan for the selection of diabetic patients who have a basal insulin need, and a clinical method by which this requirement may be measured are presented in this paper.

Patients from the Diabetic Service of the Los Angeles County General Hospital were used for this study of basal insulin requirement. All were uncomplicated diabetics who had been in the hospital for several weeks. Protamine zinc insulin, if used, was discontinued 36 to 48 hours before tests were made. During the 14 hours immediately preceding the tests and during the period in which they were made, the patients received no food. Blood sugar

determinations were done on oxalated venous blood by the Folin-Wu micro-method, except those done during the fasting period which were done by the Benedict method. U10 regular insulin, measured with a 0.25 cc. syringe, was used for the basal insulin determination to insure accurate measurement of the small doses.

The diabetics studied were easily separated into two groups by the results of blood sugar determinations made during a fasting period which extended from 7 A.M. to 1 P.M. The basal insulin requirement of severe diabetics is clearly indicated by a rise of the blood sugar during the fasting state (Table 1) even with regular

TABLE 1.—BLOOD SUGAR CONCENTRATIONS* OF FASTING SEVERE DIABETICS.
(Patients fasting 14 hours before and during test.)

Time.	J.D., 660-551 Male 56.	F.T., 706-586 Female 14.	F.B., 698-247 Female 13.	W.D., 233-944 Male 33.	B.P., 629-381 Female 15.	E.T., 669-461 Male 14.
Midnight .	No insulin	10 units†	20 units†	5 units†	25 units†	No insulin
A.M. . .	202	100	70	58	260	136
8 A.M. .	...	169	...	...	303	
9 A.M. .	241	198	241	130	345	222
10 A.M. .	...	200	...	...	323	
11 A.M. .	290	206	267	208	400	185
Noon . .	...	204	...	...	435	
1 P.M. .	323	...	303	252	...	182

* Milligrams per 100 cc. † Regular insulin.

insulin at midnight. Individual rises varied from 44 to 233 mg. in 6 hours. In contrast to this the curves which resulted from determinations of the blood sugar in mild diabetics who were fasting and had no insulin at midnight, were flat, and indicated no basal insulin requirement (Table 2). This is a simple method for determining which patients have a basal insulin requirement.

TABLE 2.—BLOOD SUGAR CONCENTRATIONS* OF FASTING MILD DIABETICS.
(Patients fasting for 14 hours before and during test.)

Time.	F.F., 663-516, Male 32.	G.B., 645-568, Female 24.	M.B., 390-488, Female 33.	M.H., 712-574, Female 32.
Midnight	...	...	...	155
3 A.M.	...	...	...	174
7 A.M.	118	116	105	167
9 A.M.	103	152	100	174
11 A.M.	91	149	87	167
1 P.M.	86	132	94	174

* Milligrams per 100 cc.

Others[6,7] have recognized the fact that the blood sugar of the severe diabetic rises during the fasting state, and particularly at night. The therapeutic importance of this rise, however, has not been emphasized and few quantitative determinations of the requirement have been made.[1,4]

Quantitative measurement of the basal insulin requirement of 7 patients, who were found to have a rise of blood sugar during the fasting state, were made. The results in 4 of these patients are summarized in Tables 3 to 6. A detailed analysis of one record (B.P. 629–381, Table 3, Sect. 2), will illustrate the method used:

TABLE 3.—PATIENT B.P., 629–381, WHITE FEMALE, AGE 15.
(Patient fasting for 14 hours before and during each test.)

SECTION 1. Blood sugars fasting.			SECTION 2. Basal insulin determination subcut.* regular insulin.			SECTION 3. Basal insulin determination I.V.† regular insulin.			SECTION 4. Basal insulin determination with one dose PZI.‡		
4-10-40. Time.	Bl. sug., mg. per 100 cc.	Reg. insulin.	4-19-40. Time.	Bl. sug., mg. per 100 cc.	Reg. insulin.	4-23-40. Time.	Bl. sug., mg. per 100 cc.	Reg. insulin, I.V.	5-7-40. Time.	Bl. sug., mg. per 100 cc.	PZI.
Midnight	..	25	Midnight	..	30	Midnight	..	30	Midnight	..	30 (subc.)*R.I.
7 A.M.	260		7:08 A.M.	148.1		7:30 A.M.	156.2	(subc.)	7:15 A.M.	98	
8	303		7:10	..	2½	8:00	..	4	7:16	..	20 PZI
9	345		8:08	175.4		8:28	163.9		9:30	95.2	
10	323		8:10	..	2½	9:01	..	2	11:30	114.9	
11	400		8:43	170.9		9:27	137.0		1:40 P.M.	163.9	
12	435		9:10	..	2½	10:00	..	2	3:20§	178	
			9:40	190		10:28	120.5				
			10:09	..	3	10:58	..	2	7:00 A.M. to 3:20 P.M.—6.75 gm. sugar in urine.		
			10:35	190		11:27	111.1				
			11:08	..	3	11:59	..	2			
			11:34	190		12:27 P.M.	106.4				
			12:14 P.M.	..	3	1:00	..	2			
			12:40	150		1:27	104.2				
			1:20	111		2:00	..	2			
			6 A.M. to 1:30 P.M.—7.6 gm. sugar in urine.			2:26	86.2				
						7:30 A.M. to 2:30 P.M.—no sugar in urine.					

* Subcut. = subcutaneously in all tables.
† I.V. = intravenous in all tables.
‡ PZI = protamine zinc in all tables.
§ This does not represent end of PZI activity, although test was stopped at this point.

1. *Preparation for Test:* (*a*). The patient received no food for 14 hours before starting the test, nor during the test.

(*b*). Thirty units of regular insulin were given at midnight before the test to insure a blood sugar within the normal range at the start of the test. The amount of insulin required at midnight varies with the severity of the case, and the previous level of control. The least severe diabetics require 5 to 10 units, the most severe 25 to 30 units.

2. *The Test:* (*a*). Regular insulin was given subcutaneously at hourly intervals and blood sugar determinations were made at hourly or half-hourly intervals.

(*b*). The insulin dosage was changed as indicated by a rising or falling level of the blood sugar. As the blood sugar rose from 148.1 to 190 mg. per 100 cc. from 7:08 A.M. to 9:40 A.M. with the use of 2½ units per hour, the amount was increased to 3 units per hour. This

TABLE 4.—PATIENT F.B., 698–247, WHITE FEMALE, AGE 13.
(Patient fasting for 14 hours before and during each test.)

SECTION 1. Blood sugars fasting.			SECTION 2. Basal insulin determination I.V. regular insulin.			SECTION 3. Basal insulin determination with one dose PZI.		
4-27-40. Time.	Bl. sugar, mg. per 100 cc.	Insulin.	5-4-40. Time.	Bl. sugar, mg. per 100 cc.	Insulin.	5-7-40. Time.	Bl. sugar, mg. per 100 cc.	Insulin.
Midnight	...	20	Midnight	...	20* (subcut.)	Midnight	...	20 R.I.
7 A.M.	70		7:40 A.M.	142.8		7:20 A.M.	106.9	
9	241		8:17	...	2½	7:21	...	10 PZI
11	267		8:44	146.0		9:35	106.9	
1 P.M.	303		9:18	...	1½	11:30	125.0	
			9:40	108.7		1:40 P.M.	119.7	
			10:16	...	1½	3:25	129.0	
			10:38	80.2				
			11:16	...	—	7:30 A.M. to 3:15 P.M.—no sugar in urine.		
			11:44	117.6				
			12:16 P.M.	...	1¼			
			12:42	137.0				
			1:18	...	1¼			
			1:41	94.3				
			2:15	...	1½			
			2:38	95.7				
			7:30 A.M. to 2:45 P.M.—no sugar in urine.					

* Subcutaneously.

TABLE 5.—PATIENT J.D., 669–551, WHITE MALE, AGE 56.
(Patient fasting 14 hours before and during each test.)

SECTION 1. Blood sugars fasting.			SECTION 2. Basal insulin determination subcut. regular insulin.			SECTION 3. Basal insulin determination I.V. regular insulin.			SECTION 4. Basal insulin determination with one dose PZI.		
4-13-40. Time.	Bl. sug., mg. per 100 cc.	Insulin.	4-20-40. Time.	Bl. sug., mg. per 100 cc.	Insulin.	4-23-40. Time.	Bl. sug., mg. per 100 cc.	Insulin.	5-7-40. Time.	Bl. sug., mg. per 100 cc.	Insulin.
Midnight		No	Midnight		10	Midnight		15* (subcut.)	Midnight		8 RI.
7 A.M.	202	insulin	7:13 A.M.	204.1		7:28 A.M.	185.2		7:30 A.M.	261.4	
9	241		7:20	...	1	7:56	...	1.50	7:31	...	6 PZI
11	290		8:10	204.1		8:25	169.5		9:35	285.6	
1 P.M.	323		8:15	...	2	8:57	...	0.75	11:30	256.0	
			8:47	200.0		9:24	148.1		1:40 P.M.	215.0	
			9:15	...	3	9:57	...	0.75	3:30	182.0	
			9:45	166.7		10:25	137.9				
			10:15	...	1	10:56	...	0.75	7:30 A.M. to 3:30 P.M.—13.1 gm. sugar in urine.		
			10:43	150.4		11:24	141.8				
			11:40	116.3		11:56	...	0.75			
			12:45 P.M.	96.1		12:24 P.M.	137.9				
			1:40	98.0		12:57	...	0.75			
			2:45	137.0		1:24	140.8				
			3:50	169.5		1:57	...	0.75			
			6:00 A.M. to 3:45 P.M.—no sugar in urine.			2:23	122.7				
						7:00 A.M. to 2:30 P.M.—no sugar in urine.					

* Subcutaneously.

amount was too great as the blood sugar fell from 190 to 111 mg. per 100 cc. between 4½ and 6 hours. Part of this fall, however, was due to cumulative effect of hourly injections. The cumulative effect with hourly injections of regular insulin manifests itself between 4 and 6 hours, so the test should be run for at least 6 hours.

TABLE 6.—PATIENT F.T., 706–586, MEXICAN FEMALE, AGE 14.
(Patient fasting 14 hours before and during each test.)

SECTION 1. Blood sugars fasting.			SECTION 2. Basal insulin determination Subcut. regular insulin.			SECTION 3. Basal insulin determination I.V. Regular insulin.		
4-10-40. Time.	Blood sugar, mg. per 100 cc.	Insulin.	4-19-40. Time.	Blood sugar, mg. per 100 cc.	Insulin.	5-4-40. Time.	Blood sugar, mg. per 100 cc.	Insulin I.V.
Midnight	...	10	Midnight	...	20	Midnight	...	20* (subcut.)
7 A.M.	160	R.I.	7:12 A.M.	215.0		7:38 A.M.	160.0	
8	169		7:14	...	1½	8:16	...	2½
9	198		8:12	206.2		8:41	149.2	
10	200		8:14	...	2	9:15	...	1½
11	206		8:45	198.1		9:37	130.7	
12	204		9:12	...	1½	10:14	...	1½
			9:41	192.3		10:37	100.0	
			10:10	...	1½	11:16	...	1½
			10:37	185.0		11:41	144.9	
			11:10		1½	12:14 P.M.	141.8	
			11:35	142.0		1:15	...	1½
			12:40 P.M.	148.0		1:37	119.0	
						2:14	...	1½
			6 A.M. to 12 P.M.—5.3 gm. sugar in urine.			2:33	115.0	
						7:30 A.M. to 2:45 P.M.—no sugar in urine.		

* Subcutaneously.

(*c*). The requirement was calculated from the above as 2½+ units per hour (16.5 units of insulin required in 6 hours, with the blood sugar 148.1 mg. per 100 cc. at the start and 111 mg. per 100 cc. at the end of the experiment).

The basal insulin determination in the same patient when regular insulin was given intravenously is seen in Sect. 3, Table 3. This was done to eliminate the factor of variability in the rate of absorption. In general, the method and results are similar. However, the initial intravenous dose was doubled because of mathematical considerations concerning the rate of destruction of intravenous insulin.[2b]

The rate was between 2 and 2½ units per hour by the intravenous route. (Sixteen units of insulin were given in 6 hours; the blood sugar was 156 mg. per 100 cc. at the start and 86.2 mg. per 100 cc. at the end of the test. The degree of fall in blood sugar was due to slightly too much hourly insulin, plus cumulative effect.)

The basal insulin determination by means of hourly injections of regular insulin (given either intravenously or subcutaneously), as

illustrated, is not practical for clinical use. For this reason we have devised a clinically applicable method.

We have found in a study of a group of 11 patients that there is a rough, general correlation between the total 24-hour insulin dose (disregarding diet) and the basal insulin requirement (Table 7). (The

TABLE 7.—TOTAL INSULIN DOSAGE AND BASAL REQUIREMENT PER HOUR.

Patient.			Total insulin dosage, 24 hours.	Carbohydrate.	Protein.	Fat.	Basal insulin requirement per hour, unit.
1. W.D.	M	33	30	225	85	80	½
2. G.B.	M	20	45–50	180	75	75	¾–1
3. J.D.	M	56	40	200	85	90	¾
4. E.T.	M	14	85	250	85	80	1
5. U.T.	F	18	65	100	60	80	1
6. J.Z.	M	27	50	150	60	75	1
7. F.B.	F	13	70	175	70	80	1¼
8. F.T.	F	14	80	175	70	80	1½
9. P.Q.	M	23	70	180	75	100	2
10. B.P.	F	15	95	150	65	80	2½
11. M.F.	F	44	130	150	75	100	3

dietary intakes varied from 1500 to 2150 calories.) This correlation may be summarized as follows:

1. When the 24-hour requirement of insulin is from 40 to 50 units the basal insulin requirement is between 0 and ¾ units per hour.

2. When it is 50 to 70 units the basal insulin requirement is between 1 to 1¼ units per hour.

3. When it is 70 to 100 units the basal insulin requirement is between 1½ to 2½ units per hour.

4. And when it is more than 100 units the basal insulin requirement is more than 3 units per hour.

After a severe diabetic is moderately well controlled by 3 or 4 injections of regular insulin daily an estimate of the probable basal insulin requirement can be made from the total dose, as tabulated above. To check the correctness of this estimated amount the following simple procedure can be performed by giving one injection of protamine zinc insulin and making 4 or 5 blood sugar determinations. The method is illustrated by Patient F. B. 698–247, Table 4, Sect. 3.

1. *Preparation for Test:* (*a*). The patient received no food within the 14 hours preceding and none during the test.

(*b*). Twenty units of regular insulin were given at midnight before the test to insure a blood sugar within the normal range at the start of the test.

2. *The Test:* (*a*). Ten units of protamine zinc insulin were given at 7:21 A.M. and blood sugar determinations were made at intervals of 2 hours during the next 8 hours. (The amount of protamine zinc insulin given was calculated as follows: The patient was receiving a

total of 70 units of regular insulin daily. From this figure the probable requirement was estimated as $1\frac{1}{4}$ units of regular insulin per hour, or 10 units of regular insulin for 8 hours. Empirically the same dose of protamine zinc insulin in one injection has been found to be effective in controlling the basal requirement during the night. This fact is supported by the statement of Lawrence,[3] who says that 10 units of protamine zinc insulin last from 6 to 8 hours and 20 units 12 hours.)

(*b*). As seen by the chart there was a very negligible rise of the blood sugar—22 mg. per 100 cc.—from 9:35 A.M. to 3:25 P.M. This is in sharp contrast to the rise from 70 to 303 mg. per 100 cc. in 5 hours without insulin, seen in Sect. 1 of Table 4. The patient had received 20 units of insulin at midnight before each test. Thus 10 units of protamine zinc insulin covered the basal requirement for at least 8 hours in this patient.

The basal insulin requirement was determined with 1 dose of protamine zinc insulin in 3 patients in whom the more exact, tedious method with hourly injections of regular insulin had already been done. The requirement was found to be approximately the same, as seen in Table 3, Sect. 4; Table 4, Sect. 3; Table 5, Sect. 4.

Protamine zinc insulin is used to cover the basal requirement in preference to regular insulin, because of its slow, steady absorption and plateau type of activity. The basal insulin requirement exists 24 hours of the day, but is not a therapeutic problem except at night, since the insulin given to cover the diet is usually sufficient to cover the basal requirement during the day. The protamine zinc insulin to cover the night basal requirement is best given at the same time as the pre-dinner regular insulin. The amount needed is determined by multiplying the hourly requirement by the number of hours (12 to 15 hours) between dinner and breakfast as discussed above. Larger doses (40+ units) of protamine zinc insulin given before breakfast to cover the night basal requirement may cause hypoglycemia in the postabsorptive period at night.

The importance of the measurement of the basal insulin requirement lies in its therapeutic usefulness. We have demonstrated its value in regulating severe diabetics never previously well controlled.[4] It is obviously advantageous for a severe diabetic to start the day with a normal blood sugar level.

Summary. 1. The basal insulin requirement of 5 severe diabetics was determined with regular insulin using both subcutaneous and intravenous injections. This requirement varied from $\frac{1}{2}$ to $2\frac{1}{2}$ units of insulin per hour.

2. A clinical method of measuring the basal insulin requirement with one injection of protamine zinc insulin is outlined.

3. The value of a basal insulin determination and its use in the control of the severe diabetic is discussed.

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INTERCAPILLARY GLOMERULOSCLEROSIS (KIMMELSTIEL–WILSON) AND THE NEPHROTIC SYNDROME IN DIABETES MELLITUS.

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In 1936 Kimmelstiel and Wilson[4] described a distinctive lesion of the renal glomeruli and called attention to its association with a clinical complex of diabetes mellitus, hypertension and a nephrotic syndrome. To this lesion they gave the name "intercapillary glomerulosclerosis" because they believed it to be a sclerotic thickening of the intercapillary connective tissue. Apart from its occurrence in the intracapillary type of glomerulonephritis, the lesion was found in only 8 cases, of which 7 were diabetic, out of the entire post-mortem material which they studied. They concluded that "only a small proportion of diabetics appear to show this lesion."

In 1938 Anson[2] studied the kidneys in 900 cases, and found the changes characteristic of "intercapillary glomerulosclerosis" only 6 times. He confirmed its correlation with diabetes and hypertension but in only 2 instances with the nephrotic syndrome. Since then 2 more small series of cases have been published in which the clinical data have been more completely presented.[3,5] They support the thesis that the lesion described by Kimmelstiel and Wilson is almost always associated with diabetes, with hypertension, with profuse albuminuria and often with a nephrotic syndrome. Nonetheless, further study is warranted to ascertain whether the lesion occurs among non-diabetics, apart from glomerulonephritis, and whether in the diabetic cases it is invariably associated with the clinical findings mentioned above. In undertaking this study, we were stimulated by our previous interest in the association of a nephrotic

* Work done during tenure of George Blumenthal, Jr., Fellowship in Pathology.

picture with diabetes[8] and by the hope that some further light might be shed upon the problem of the pathogenesis of the nephrotic syndrome.

The *postmortem material* studied comprises cases falling into the following clinical categories: (Table 1).

TABLE 1.—CLINICO-PATHOLOGIC CORRELATION.

Clinical classification.	No. of cases.	Kimmelstiel-Wilson lesions.					
		Present.	Grade of development.				Absent.
			1.	2.	3.	4.	
Control series: non-diabetic, non-hypertensive	100	0	..	..	..	..	100
Control series: non-diabetic with hypertension	100	1	..	..	1	..	99
Diabetic series	105	35	16	9	8	2	70
Group 1: no hypertension; no renal complication	60	12	10	2	..	..	48
Group 2: hypertension; no renal complication	27	9	4	4	1	..	18
Group 3: partial or complete renal syndrome	18	14	2	3	7	2	4*

* Includes 1 case of renal amyloidosis.

A. One hundred consecutive non-diabetic control cases, without hypertension. All ages were included.

B. One hundred consecutive non-diabetic cases with hypertension, all 40 years of age or more. A blood pressure of 160/90 or more was considered abnormal.

C. One hundred and five consecutive cases of diabetes 40 years of age or older. These cases were classified clinically into three groups. The first and second groups included those with slight or no evidence of renal damage. The second group differed from the first in the presence of hypertension. The third group comprised cases with hypertension and with definite signs of renal damage, often with partial to complete development of a nephrotic syndrome.

The diabetic kidneys were graded as to the degree of development and extent of the Kimmelstiel-Wilson lesion. The 1+ kidneys averaged 1 to 5 lesions per microscopic section, whereas the 4+ kidneys contained lesions in almost every glomerulus. The diabetic cases which had been classified solely on clinical grounds were then correlated with these pathologic findings.

Special stains for collagenous and elastic tissue (Mallory's aniline blue, phosphotungstic acid hematoxylin, azocarmine, and Weigert's combined with Van Gieson) and for amyloid and fat deposits were applied when indicated.

The *clinical material* consists of 11 additional cases which have

been reported elsewhere.[8] These illustrate the occurrence of a nephrotic syndrome in diabetes. Each of the 11 cases would be classified clinically in Group 3 (Table 1) as noted above. Four of these cases have been autopsied and the kidneys studied and graded as to the development of the glomerular lesion in the manner already described.

Results. *Clinico-pathologic Correlation.* Table 1 shows that the Kimmelstiel-Wilson lesion was absent from the kidneys of all the non-diabetic control cases without hypertension. This group included a wide range of medical and surgical conditions. In the second control series of non-diabetic cases with hypertension, only 1 out of 100 revealed the specific glomerular change. The special interest which attaches to the unusual occurrence of this lesion in the absence of diabetes warrants the presentation of this case in some detail:

Intercapillary Glomerulosclerosis in a Case of Hypertension Without Diabetes.

Case 451955; PM 11419. A 51-year-old Italian housewife with a 15-month history of hypertension, edema and dyspnea. No personal or family history of diabetes. Examination revealed obesity, slight dyspnea. Fundi: arteriovenous compression, hard exudates and hemorrhages. Signs of fluid in both pleural cavities. Edema of abdominal wall, upper and lower extremities. B.P. 160/90. Laboratory findings: Hemoglobin, 86%; urine: 3+ albumin, moderate casts; Esbach: 4 gm. per liter. No glucose in 3 specimens. Venous pressure 15 cm. Blood urea N 60 mg. per 100 cc.; total protein 6 gm. per 100 cc.; glucose 85 mg.; cholesterol 240 mg. Patient's course was one of progressive cardiac failure. Autopsy: hypertrophy and dilatation of ventricles; diffuse myofibrosis cordis; moderate sclerotic narrowing of LAD coronary artery branch; congestion of viscera; mild benign nephrosclerosis. The kidneys weighed 360 gm. together, the capsules stripping with slight difficulty, leaving a very finely granular purplish-gray surface. Cut surface showed sharp cortico-medullary differentiation. Renal sections: much cortical atrophy. The Kimmelstiel-Wilson lesions were typical and were of Grade 3. Marked arteriolosclerosis. Moderate amount of fat in arterioles and convoluted tubules (Fig. 1.)

Apart from the consecutive series of control cases a second instance of the occurrence of the advanced Kimmelstiel-Wilson lesion in nephrosclerosis without diabetes was accidentally encountered. As in the case just presented, there were evident signs of renal damage such as profuse albuminuria, tendency to hypoproteinemia, marked edema and nitrogen retention. Although arteriolosclerosis of the kidneys and cardiac failure might in each instance have been sufficient to cause these phenomena, it is probable that as in the diabetic cases the "intercapillary glomerulosclerosis" has contributed to the renal picture.

In the series of 105 diabetics the Kimmelstiel-Wilson lesion was found in 35 cases. Table 1 shows the close correlation in the degree and extent of the lesion with the degree of development of the renal syndrome. Thus the lesion was present in 14 of 18 cases showing definite clinical signs of a renal complication (Group 3). In 9 of

these the lesion was in an advanced stage. In contrast, only 12 of the 60 diabetics without hypertension or renal damage (Group 1) showed the lesion and then generally in an incomplete stage of development. In such cases the lesion might even be limited to a single glomerulus in a microscopic section. However, they are identical with those described by Kimmelstiel and Wilson and they cannot be distinguished from those seen in sections containing other lesions in a more advanced and obvious stage. The occurrence of this form of glomerulosclerosis in the absence of profuse albuminuria, edema, hypertension, eye ground changes, or other criteria of the renal

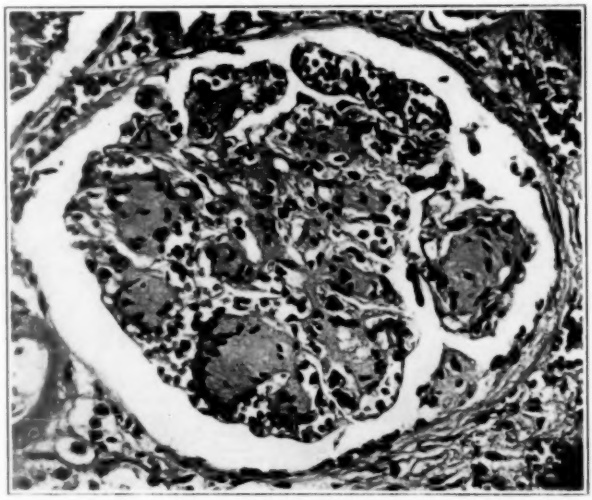

FIG. 1.—PM, 11419. Intercapillary glomerulosclerosis in a case of hypertension *without* diabetes.

complication with which it has come to be associated, is of some theoretical importance. One of these cases may deserve detailed presentation to illustrate this point more clearly.

Intercapillary Glomerulosclerosis in Diabetes Without Hypertension or Renal Syndrome.

Case 421959; PM 10797. A 67-year-old Jewish housewife with a past history of several gall bladder attacks, admitted with the complaint of anorexia, asthenia and jaundice of 4 weeks' duration. Diabetes of 10 years' duration controlled by diet alone. Physical examination: B.P. from 120/60 to 150/60. Fundi negative. Precordial systolic murmur. Liver huge, slightly tender. No edema. Moderate icterus. Laboratory findings: Hemoglobin 60%. Urine: albumin faint trace, trace and 1+ on three occasions; occasional casts. Blood urea nitrogen 23 mg. per 100 cc.; glucose 220 mg.; cholesterol 1000 mg.; total protein 7.1 mg. Icterus index 20. Patient died several weeks after operation because of subdiaphragmatic abscess. Procedure was cholecystectomy and choledochotomy for stone. Autopsy: moderate coronary atherosclerosis; mild benign nephrosclerosis; left subdiaphragmatic abscess. The kidneys weighed 325 gm. together and

showed fine granularity of the surface. Histologic sections: slight degree of arteriosclerosis and arteriolosclerosis. The Kimmelstiel-Wilson lesions were of Grade 2 (Fig. 2).

Cases such as these suggest strongly that the Kimmelstiel-Wilson lesion does not depend upon the presence of appreciable nephrosclerosis for its development and that it may occur without clinical evidence of significant renal damage. Its relationship with diabetes is all the more emphasized inasmuch as this is the one element of the triad of diabetes, hypertension and albuminuria[6] which is almost constantly present. However, as we have already seen, this too may in rare instances be absent.

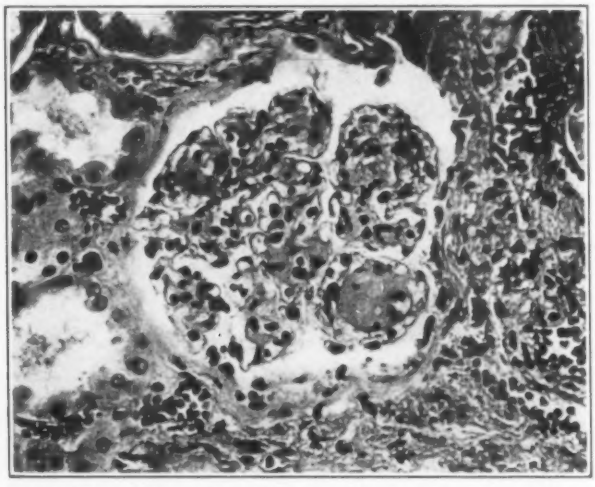

FIG. 2.—PM, 10797. Intercapillary glomerulosclerosis in a case of diabetes *without* hypertension or the elements of the nephrotic syndrome.

The Clinical Syndrome With Advanced Glomerulosclerosis. The salient clinical features of 10 cases from the consecutive series of diabetics in which the Kimmelstiel-Wilson lesions were found in an advanced stage, Grades 3 or 4, are shown in Table 2. No constant clinical syndrome characterizes these cases, although a tendency to marked albuminuria and hypoproteinemia may be present. The clinical findings in this type of case often may be distinctive enough to warrant a diagnosis of "intercapillary glomerulosclerosis." Coronary thrombosis, heart failure or peripheral vascular disease may dominate clinical attention. However, in 3 instances (Cases 8, 9, and 10; Table 2) the renal complication was prominent enough to be readily recognized clinically. Case 10 illustrates the fullest development of the renal syndrome with marked edema, lowered total blood proteins, increased blood cholesterol, hypertension, and termination in uremia. Such a clinical syndrome occurring in a middle-aged mild diabetic warrants the diagnosis of this type of renal lesion.

TABLE 2.—ADVANCED GLOMERULOSCLEROSIS (KIMMELSTIEL-WILSON) IN DIABETES. CLINICAL FEATURES OF TEN CONSECUTIVE AUTOPSIED CASES.

Case No.	Age.	Sex.	Diagnosis and clinical course.	Diabetes.		Blood pressure.	Edema	Eye ground changes.	Cardiac failure.	Urine.				Blood.				
				Duration, yrs.	Insulin need, units.					Albumin.	Sp. gr., max.	R.B.C.	Casts.	Glucose.	Total protein, alb. glob.	Cholesterol.	Urea nitrogen.	Hgb., %
413717 (1)	60	F	Essential hypertension Fractured neck of femur	16	15	240/140	0	±	±	2+ 4 G/L	1.014	0	±	210	N.R.	600	39	52
374641 (2)	60	M	Diabetic gangrene Arteriosclerotic heart disease	14	0	168/92	N.R.	3+	3+	3+	1.018	0	2+	190	N.R.	N.R.	45	55
413383 (3)	55	F	Coronary thrombosis Multiple carbuncles	15	0	160/90	1+	Myopia	1+	1+	1.018	0	±	550	5.6 (2.8, 2.8)	310	34	71
371058 (4)	65	F	Diabetic gangrene Bronchopneumonia	3	10	195/80	0	N.R.	0	4+	1.015	0	±	255	5.6 (3.1, 2.5)	270	24	N.R
447456 (5)	70	M	Arteriosclerotic heart disease Coronary thrombosis Congestive failure	2	0	160/90	2+	2+	2+	4+ 5 G/L	1.024	0	4+	230	6.0	315	38	60
453119 (6)	52	F	Gas gangrene Diabetic retinitis Uremia	6	0–10	130/72	2+	4+	3+	4+	1.034	0	±	230	5.6	N.R.	50	74
395731 (7)	52	F	Pyelonephritic contracted kidney Cardiac failure Coronary thrombosis	5	20	220/95	0	N.R.	3+ (left)	Trace	1.012	±	0	205	N.R.	450	39	45
398307 (8)	51	F	Arteriosclerotic heart disease Old coronary thrombosis	10	40	150/100	4+	3+	4+	3+	N.R.	0	0	280	5.2 (2.5, 2.7)	535	16	90
385838 (9)	61	F	Hypertensive heart disease Lobar pneumonia	11	20–40	240/116	3+	± Myopia	1+	3+	1.028	0	±	215	5.3 (2.8, 2.5)	830	30	62
449648 (10)	55	F	Arteriosclerotic heart disease Uremia Peripheral neuropathy	5	25	190/100	3+	1+	2+	4+ 8 G/L	1.014	0	3+	220	4.7 (2.7, 2.0)	440	131	75

G/L in albumin column = grams per liter (Esbach).

As previously reported,[8] a syndrome closely simulating the clinical picture and course of chronic glomerulonephritis is not an uncommon occurrence among middle-aged or elderly diabetics. Such cases are especially characterized by the development of a nephrotic syndrome. Table 3 presents 11 such cases, of which only 4 (Cases 1 to 4) have been autopsied, all showing the Kimmelstiel-Wilson lesions in an advanced stage, Grades 3 or 4.

The following case illustrates the characteristic clinical course of these cases which develop the complete renal syndrome:

Intercapillary Glomerulosclerosis in a Diabetic With Hypertension and Nephrotic Syndrome.

History. Adm. 437064. The patient, a 55-year-old negress, had been under observation in the diabetes clinic since 1935. Her family history was of no significance. Her past history was negative. There was no history of scarlet fever, kidney disease, or of hypertension. She complained of marked loss of weight, moderate polydipsia, and polyuria of several months' duration. Five per cent glucose and a trace of albumin were discovered in the urine. Her blood pressure was 158/90. Her diabetes was mild and readily brought under control on a diet of 120–60–60 with 10 units of regular insulin daily.

A tendency to unusually rapid weight gains was noted within the first few months of observation; but it was not until 1937, after a rather long lapse in clinic attendance, that the appearance of edema was first observed. At this time, she also had shooting pains in the left leg and a sensation of deadness in both hands. She had had swelling of the legs for several months but no dyspnea or precordial pain. There was a hypertension of 190/90, a tachycardia of 116, and moderate pretibial pitting edema.

In the light of previous experience with similar cases, the cause of the edema was forthwith sought in hypoproteinemia. The blood total protein was found to be 4.4 gm. per 100 cc. with albumin and globulin fractions each 2.2 gm. per 100 cc. Blood cholesterol was 535 mg. per 100 cc. The urine contained a heavy trace of albumin with some casts and a rare red blood cell.

It was apparent then that the patient presented the clinical and laboratory findings of the nephrotic syndrome as seen in the course of chronic glomerulonephritis. She was referred to the hospital wards for more intensive study and therapy.

Examination. The pupils were equal, reacting to light and in accommodation. The lungs were negative; there was no evidence of pleural effusion. The heart was not enlarged. There was a regular sinus rhythm with no murmurs. The liver was palpable two finger-breadths below the costal margin. Slight dullness was present in both flanks, with a fluid wave. There was moderate dependent edema. The peripheral pulses were patent. The deep reflexes were equal and active. The blood pressure was 170/100. The fundi were described by the ophthalmologist as showing slight narrowing of the arteries. The neurologic consultant found only slight evidence of peripheral neuropathy, namely, diminution of vibration sense in both lower extremities, pain and touch being only slightly affected.

Laboratory Data. Hemoglobin 63%; R.B.C. 3,900,000; W.B.C. 7100 with a normal differential count; blood urea nitrogen 15 mg. per 100 cc., glucose 160 mg. per 100 cc., cholesterol 470 mg. per 100 cc. and total proteins 5.4 gm. per 100 cc. (albumin 2.6, globulin 2.8). The blood Wassermann reaction was negative. The urine showed from a very faint trace to 2+ albumin, the Esbach test showing as much as 2 gm. per liter. There

TABLE 3.—THE NEPHROTIC SYNDROME IN DIABETES.

Case No.	Age.	Sex.	Diagnosis and clinical course.	Diabetes.		Blood pressure.	Edema.	Eye ground changes.	Cardiac failure.	Urine.				Blood.				
				Duration, yrs.	Insulin need, units.					Albumin.	Sp. gr., max.	R.B.C.	Casts.	Glucose.	Total protein, alb. glob.	Cholesterol.	Urea nitrogen.	Hgb., %
401506* (1)	50	M	Chronic glomerulonephritis Died in uremia and heart failure	½	0	190/130	3+	3+	3+	3+ 3 G/L	1.024	1+	1+	181	4.5 (2.2, 2.3)	375	139	88
409473* (2)	44	M	Malignant hypertension(?) Chronic glomerulonephritis Death in uremia and heart failure after 2 years	1¼	0–15	220/140	2+	4+	2+	3+	1.018	0	3+	236	5.1 (2.9, 2.2)	650	61	62
414048* (3)	56	F	Chronic glomerulonephritis Death in uremia 2 years after onset	12	0–15	200/110	4+	4+ blindness	3+	4+ 8.5 G/L	1.020	2+	1+	175	4.4 (2.2, 2.2)	750	75	53
437064*† (4)	55	F	Chronic glomerulonephritis Death after 2 years in uremia and heart failure	4	0–20	230/120	4+	2+	3+	3+ 2.5 G/L	1.017	1+	1+	260	4.4 (2.2, 2.2)	535	114	52
383304 (5)	54	F	Chronic glomerulonephritis Death in uremia 3 years after onset	7	25–30	210/90	4+	4+	*	4+ 6.6 G/L	1.016	0	1+	265	4.8 (2.4, 2.4)	775	73	43
372041 (6)	50	F	Chronic glomerulonephritis Hypertensive heart disease Death in heart failure after 3 years	20	15–30	180/90	4+	2+	4+	3+	1.012	*	1+	310	5.6 (3.2, 2.4)	675	50	60
434532 (7)	49	M	Chronic glomerulonephritis	10	0–20	200/110	2+	2+	1+	3+ 3 G/L	1.022	*	1+	155	4.2 (1.8, 2.4)	500	51	80
429499 (8)	73	M	Chronic glomerulonephritis Essential hypertension	5	0	200/100	2+	3+	0	2+	1.018	2+	2+	230	5.2 (3.1, 2.1)	410	40	70
440450 (9)	48	F	Chronic glomerulonephritis Death in uremia 2 years after onset	½	0	200/90	3+	2+	0	3+	1.023	*	3+	180	4.9 (2.8, 2.1)	625	153	70
457272 (10)	46	F	Hypertensive heart disease Congestive heart failure Alive 4 years after onset	9	0–30	210/110	3+	2+	3+	3+ 4 G/L	1.020	0	3+	200	4.6 (1.9, 2.7)	500	84	80
38–520 (11) (O.P.D.)	66	M	Diabetic glomerulosclerosis	6	0	212/112	3+	*	0	4+	1.016	*	1+	280	4.8 (3.4, 1.4)	370	12	72

* Cases autopsied all showing lesions of intercapillary glomerulosclerosis, Grades 3 or 4.
† Case presented in text.
G/L in albumin column = grams per liter (Esbach).

was an occasional hyaline cast and a rare red blood cell. The urine concentrated to a specific gravity only of 1.017.

The venous pressure was 5 cm.; circulation time measured by the saccharine method was 12 seconds. These determinations gave the clinical impression that circulatory failure played no rôle whatsoever in the production of the edema. The electrocardiogram showed left axis deviation *QRS* complex slightly slurred with moderately low voltage, and T_1 isoelectric.

Course. Under observation for a period of 19 days, the patient's diabetes was brought under control on a regimen of 150 gm. CHO, 150 gm. protein, and 120 gm. fat without insulin. The edema disappeared on this diet and bed rest, without the use of diuretics. The albuminuria decreased. The total protein rose to 6.2 gm. per 100 cc., but of this the albumin fraction remained 2.5 gm.

Because of the ready response to treatment, the patient was discharged with the diagnosis of diabetes mellitus and essential hypertension. The edema and hypoproteinemia were thought to be due to malnutrition caused by strict adherence to a limited diabetic diet.

She remained under close observation in the diabetic clinic and two subsequent hospital admissions during the next 2 years. The clinical course was such as to modify the former somewhat optimistic impression as evidence of cardiac and renal failure appeared. Despite faithful adherence to a high protein regimen, there was a reaccumulation of edema, the low blood proteins persisting (5 gm. per 100 cc., albumin 2.2, globulin 2.8), together with an increased blood cholesterol level (765 mg. per 100 cc.) and profuse albuminuria.

Two further laboratory findings are to be noted. A Congo red test showed only 35% retention, indicating the absence of amyloidosis. A glucose tolerance test confirmed the presence of moderate diabetes.

The blood pressure tended to rise, reaching 230/120; marked hypertensive retinopathy with hemorrhages and exudates appeared; there was increasing evidence of cardiac enlargement and insufficiency. In the last few months of observation, azotemia set in with a blood urea nitrogen rather rapidly rising to 114 mg. per 100 cc. The patient was discharged from the hospital in a state of suburemia and several weeks later she died in coma.

Necropsy Findings. General anasarca was present. The heart was enlarged, weighing 500 gm. The lungs were congested and edematous. The liver was congested. The pancreas showed postmortem autolysis. The kidneys were distinctly enlarged, weighing 200 gm. each. The capsules stripped easily leaving a yellowish-gray surface, smooth except for small foci showing the finest granularity. The cut surface revealed a yellowish-gray cortex, fully 6 mm. thick, which was fairly well demarcated from the medulla. The glomeruli were purple-red. Histologic sections showed widespread distribution of Kimmelstiel-Wilson lesions involving almost every glomerulus. There was extreme arteriolosclerosis and moderate to marked arteriosclerosis. There was much fat in the walls of the thickened, hyalinized arterioles and a moderate amount in the epithelium of the convoluted tubules, the capillary loops of the glomeruli, and in Bowman's space. The Kimmelstiel-Wilson lesions were graded 4+.

Differential Clinical Features. The following clinical features of cases of this type (Table 3) deserve special emphasis: 1, Age group: all 11 patients were 44 years of age or over. 2, Type of diabetes: the diabetes was mild, requiring little or no insulin for adequate control. 3, Chronologic relationship of the diabetes and the renal syndrome: This is difficult to state categorically for both conditions are characterized by insidiousness of onset. The diabetes apparently

preceded the renal disease by from 5 to 20 years in 5 cases, and by 1 to 5 years in 2 cases. Of the remaining 4 patients, the diabetes was discovered several months before the renal disease in 2, whereas in 2 others, the symptoms and signs of the renal state developed a few months before the discovery of the diabetes. 4, Peripheral neuropathy: 1 of these patients (Case 6) presented such neurologic findings of severe enough degree to warrant the diagnosis of pseudotabes. In 2 others, the evidence of peripheral nerve involvement was slight (see also Case 10, Table 2). The tendency to peripheral neuropathy in these cases appears to support the hypothesis of a vascular etiology of this neural complication of diabetes.[9] 5, Hypertension: a systolic blood pressure of 190 or more, with a diastolic level about 100, was observed in all 11 patients. In 1 instance only (Case 2) was the hypertension so marked and the

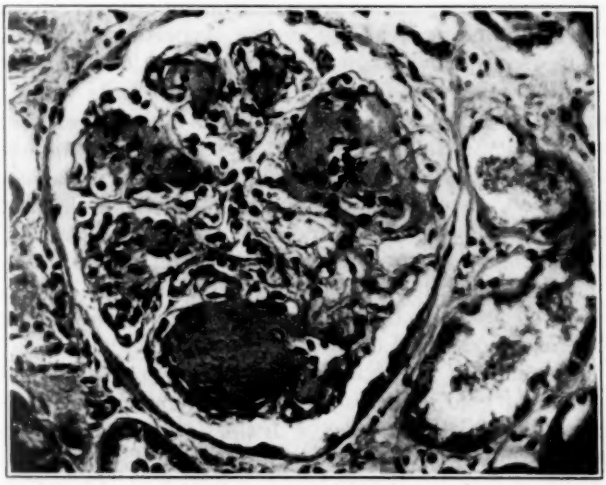

FIG. 3.—PM, 11448. Intercapillary glomerulosclerosis in a case of diabetes with hypertension and the nephrotic syndrome (Case 10, Table 2).

clinical course so accelerated as to suggest the possibility of malignant hypertension. 6, Eye ground changes: 10 of the 11 cases showed moderate to marked hypertensive retinopathy, often with evidence of concomitant diabetic changes. Edema of the disk was common in addition to severe arterial damage, hemorrhages, and exudates. These findings, in general, paralleled the course of the disease into renal failure. Retinal damage was more marked than is ordinarily seen in benign essential hypertension but quite comparable to the usual findings in advanced chronic glomerulonephritis. 7, Cardiac failure: some degree of myocardial decompensation was present in 8 of the 11 patients either coëxistent with the nephrotic picture or appearing later. 8, Azotemia: nitrogen reten-

tion was present in 10 cases, progressing to uremia in 6. 9, Prognosis: 7 of the 11 cases died within 2 to 3 years of the onset of the renal syndrome, death being due to uremia, cardiac failure or both.

These cases are not clinically identical with the nephrotic phase of chronic glomerulonephritis. Hypertension, heart failure, and severe eye ground changes are more frequently present than in the analogous stage of nephritis. An important clinical difference is that the diabetic cases fall into an older age group, usually 45 years of age or more. In contrast, the records of the Mt. Sinai Hospital from 1933 to 1938 reveal that of 93 non-diabetic patients with the nephrotic syndrome, only 10 were 45 years or older.

Discussion. The results of the investigation here presented broadly confirm the conclusion of Kimmelstiel and Wilson as to the existence of a relationship between the form of glomerulosclerosis which they described and a clinical syndrome of which the characteristic features are "diabetes, severe and widespread edema of the nephrotic type, and gross albuminuria. Hypertension is frequently present, in many cases associated with renal decompensation."[4] However, the relatively frequent occurrence of the lesion in the diabetic kidney does not appear to have been appreciated. Its presence in cases of diabetes without a renal complication strongly suggests that this type of glomerular change precedes and, when fully developed, is probably the cause of the renal syndrome. It excludes the possibility that these lesions are merely secondary to marked nephrosclerosis or somehow the result of profuse albuminuria. The parallelism of development between the Kimmelstiel-Wilson lesions and the clinical picture of the renal complication supports this concept of a causative relationship.

The occurrence of the Kimmelstiel-Wilson lesion in 2 cases of hypertension without diabetes is of great interest. The theory that diabetes is the sole etiologic factor in the development of this form of glomerulosclerosis is thus rendered untenable. This is further borne out by the fact that the lesion does not seem to occur in the course of severe diabetes and that the diabetes does not always antedate the renal syndrome. A possibility which may deserve discussion is that perhaps the same specific form of vascular damage affects both the renal glomeruli and the pancreatic islets. However, one of the authors has been unable to discover any unusual islet lesion in such cases nor is there a higher incidence of islet hyalinization in diabetes with intercapillary glomerulosclerosis than in cases without it.[1] Apparently, one must look elsewhere for the fundamental etiologic mechanism which produces both diabetes and this form of renal damage.

It is incidentally suggested[1] that the presence of intercapillary glomerulosclerosis in one-third of the diabetic cases makes this lesion of value in the postmortem diagnosis of diabetes mellitus. It is pointed out that the histologic criteria hitherto employed, such as

hyalinization of the pancreatic islets, and glycogen distribution are notoriously unreliable and difficult of interpretation. The advantages of the use of this lesion for this purpose are its ease of recognition with ordinary stains, the fact that it requires no special fixative, and, finally, that it is especially common in mild cases of diabetes where such a diagnostic clue is of particular value.[1]

The proneness of the middle-aged, mild, hypertensive diabetic to this type of renal complication, the clinical course of which may closely simulate chronic glomerulonephritis, is a fact of some clinical importance. Especially striking is the development of a partial to complete nephrotic syndrome. Young patients with severer grades of diabetes do not appear to develop this form of renal damage. A nephrotic syndrome in such patients is much more likely to be due to diffuse glomerulonephritis than to intercapillary glomerulosclerosis.[5]

Edema in the course of diabetes has in the past generally been regarded as a transient manifestation often nutritional in origin or due to therapy.[7] However, edema or persistent profuse albuminuria in the middle-aged diabetic should not be viewed lightly but should be taken as a possible warning of an impending renal complication of serious import. It is now clear that the vascular vulnerability of the diabetic may affect the kidneys as significantly as it does the heart or peripheral vessels.

Summary and Conclusions. 1. No instance of glomerulosclerosis of the Kimmelstiel-Wilson type was found in 100 consecutive cases without diabetes or hypertension.

2. In a series of 100 consecutive non-diabetic hypertensives this lesion occurred but once. The clinical and pathologic features of this case are presented in detail.

3. Intercapillary glomerulosclerosis was found in 35, or one-third, of 105 diabetics. This lesion was present in 12 of 60 diabetics *without* hypertension or a renal complication, and in 14 of 18 diabetics with clinical evidence of renal damage.

4. There appears to be a definite relationship between the degree of involvement of the kidneys by this form of glomerulosclerosis and the development of the clinical picture. However, of 10 cases with this lesion in an advanced stage, only 3 presented a complete renal syndrome.

5. The occurrence among middle-aged, mild hypertensive diabetics of a clinical syndrome closely simulating chronic glomerulonephritis, with a nephrotic phase and often with termination in renal failure, is emphasized.

6. Attention is drawn to the value of this lesion as a useful histologic criterion in the postmortem diagnosis of diabetes mellitus.

The authors wish to express their gratitude to the Montefiore Hospital and Office of the Chief Medical Examiner of New York City for permission to study autopsy material and clinical records.

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A CONSIDERATION OF CERTAIN BIOLOGICAL DIFFERENCES BETWEEN GLOMERULONEPHRITIS AND RHEUMATIC FEVER.

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Clinical,[18b,19a,32,42,48] bacteriologic,[20] and immunologic[19,22,37,39] data indicate that the initiation of glomerulonephritis is in most instances related to Group A hemolytic streptococcus infection. Comparable studies on the etiology of rheumatic fever[5b,6a,b] point to the same initiating agent. Despite the fact that the initiating agent may be the same for both diseases, it has become apparent that certain fundamental biologic differences exist between the natural history of glomerulonephritis and that of rheumatic fever. A consideration of certain of these differences is herewith presented.

Differences in the Geographic Distribution of Acute Glomerulonephritis and Rheumatic Fever. There appears to be common agreement[11,14,27,38,43,49] that rheumatic fever is more common in the northern than in the southern latitude regions of North America. In contrast, it has been shown[41] that no such geographic variation in the incidence of acute glomerulonephritis is present in the data compiled from the records of selected hospitals in the northern and southern latitude areas of North America.

When these facts are considered in the light of the geographic distribution of Group A hemolytic streptococcus infections, certain puzzling problems are raised. Coburn[6b] has reported that the hemolytic streptococcus occurs in the throat flora only rarely and in small numbers in selected individuals studied in subtropical San Juan, Puerto Rico. Morales-Otero and Pomales-Lebrón[24a] have found

that the incidence of beta-hemolytic streptococci in normal throats of inhabitants of San Juan, Puerto Rico, is 4 to 9%. Only 22.6% of the strains isolated belonged to Group A. Seasonal variations in the carrier rate were negligible. Additional data obtained by these workers are contained in the summary: "In single throat cultures from persons suffering from tropical lymphangitis, the incidence was 20 per cent, and in serial cultures, the incidence came up to 29 per cent. From persons with a history of recent sore throat, hemolytic streptococci were cultured in 30 per cent. From 100 pairs of excised tonsils, hemolytic streptococci were isolated in 33 per cent. . . . Hemolytic streptococci are not found here (San Juan) in *normal* throats as frequently as they are in New York City. On the other hand, we frequently isolate beta hemolytic streptococci from diseased tonsils, skin sores, pustules, abscesses, cases of lymphangitis, etc., and these strains are indistinguishable from those isolated in New York City." Teiger and B. C. Seegal[45] have also shown that strains of beta hemolytic streptococci isolated from the pharynx of normal individuals and patients ill of tonsillitis or acute nephritis in New Orleans are indistinguishable by the usual tests from the beta hemolytic streptococci isolated from similar individuals and patients in New York City.

Recent studies by Morales-Otero and Pomales-Lebrón[24c] in San Juan, Puerto Rico, show that significantly elevated antistreptolysin titers are found in the sera of many individuals with a history of previous pharyngitis. A previous report by these workers[24b] had indicated that hemolytic streptococcus infection played a significant rôle in recurrent tropical lymphangitis since the antistreptolysin titers in subjects ill of this disease were increased above normal levels.

Plummer[33] has presented additional evidence on immunologic grounds pointing to the presence of a considerable degree of hemolytic streptococcus infection in tropical areas. Sera obtained from students and laboratory workers in Toronto, Canada, were compared with the sera obtained from individuals in the tropical areas of Madras, Punjab, Manila, East Africa and South America in order to test their potency with respect to hemolytic streptococcus antitoxin. In subjects of all ages, 1 cc. of serum contained more than one Washington unit of streptococcal antitoxin in 64.6% of 254 Canadian, and in 93.5% of tropical sera. The mean potency of the tropical sera was significantly greater than those of the temperate zone. For subjects under 17 years of age, 44% of 50 Canadian, and 93% of 45 tropical sera contained more than one unit of antitoxin per cc. The mean potencies differed significantly. For adults, 69.6% of 204 Canadian and 93.5% of 62 tropical sera contained more than one unit of antitoxin per cc. The mean potencies were not significantly different.

These immunologic facts suggest that invasion by the Group A

hemolytic streptococcus capable of producing antitoxin as well as antistreptolysin is as prevalent in subtropical and tropical zones as in the temperate zone. It is not possible with our present state of knowledge to explain the variation in the geographic distribution of rheumatic fever and acute glomerulonephritis. However, it may be possible that the character and site of the primary focus varies for these zones. This possibility is considered later.

In summary, it is apparent that two diseases of presumable hemolytic streptococcus origin, acute glomerulonephritis and rheumatic fever, present a biologic difference with respect to geographic distribution. The incidence of rheumatic fever is conditioned by climate. The frequency of the disease is diminished in the southern as compared with the northern latitude regions of North America. This difference is not apparent in similar studies of the latitude frequency of acute glomerulonephritis. In this respect it is of considerable interest that immunologic tests for hemolytic streptococcus antitoxin and antistreptolysin indicate the presence of the hemolytic streptococcus in subtropical and tropical regions in which rheumatic fever is of low incidence and acute glomerulonephritis is of "normal incidence." The possible significance of the character of the infectious tissue focus in this difference is to be discussed elsewhere.

TABLE 1.—SEX INCIDENCE IN GLOMERULONEPHRITIS.

Reference.	Type of glomerulonephritis.	Total cases.	Male : female.	Notes.
Osman[30]	Acute	...	...	Males outnumber females in all age groups except 16–20
Seegal, Seegal and Lyttle[42]	Acute	379	2 to 1	All ages
Lyttle *et al.*[22]	Acute	116	2 to 1	95 patients under 13 yrs. of age
Schwarz, Kohn and Weiner[35]	Acute	244	2 to 1	All ages
Futcher[12]	Acute, after skin or wound infections	11	2 to 1	
Loeb *et al.*[17]	Chronic	73	2 to 1	All ages; 43% under 20 yrs. of age
Ollayos and Peters[28]	Acute	275	2 to 1	All ages

Comparison of the Sex Incidence in Glomerulonephritis and Rheumatic Fever. All reports are in agreement that acute glomerulonephritis is more common in the male. The findings of a number of workers are collected in Table 1. From these figures it may be seen that males outnumber females about 2 to 1 in all types of glomerulonephritis in the reported series.

No such unanimity as to the sex incidence in rheumatic fever is apparent from published data. It is difficult to obtain satisfactory statistics on this point probably, for two reasons: 1, the various rheumatic manifestations apparently have different sex incidence; 2, many institutions caring for rheumatic children select their cases,

having a set number of beds for each sex. A number of reports on this subject are presented in Table 2. Although there is considerable variation in the figures, there seems to be a fairly equal distribution of the two sexes for the entire group. The report of

TABLE 2.—SEX INCIDENCE IN RHEUMATIC FEVER.

Reference.	Type.	Total cases.	Male, %	Female, %	Notes.
Brooks and O'Regan[3]	Acute rh. fever	700	63	37	7% children
DeGraff and Lingg[9]	" " "	1633	56	44	Females predominate to 13 years of age
Dally[5]	" " "	300	39	61	Children only
Hench *et al.*[15]	" " "	..	40	60	
Dieuaide[10]	" " "	141	62	38	Ratio 1 to 1.36, however, when figures are corrected for hospital admissions
Swift[46b]	" " "	..	50	50	
Wilson, Lingg and Croxford[47]	Rh. heart disease	395	39	61	Children
Coombs[7]	" " "	687	34	66	All ages
St. Mary's Home[7] (Pub. cit.)	" " "	321	43	57	
Osler and MacCrae[29]	" " "	..	70	30	
Collective Investigational Reports[29] (Pub. cit.)	" " "	654	57	43	
Cabot[4]	" " "	120	53	47	Necropsied cases
	" " "	239	46	54	O.P.D. cases
	" " "	315	42	58	Total living cases
	" " "	150	35	65	Mitral stenosis
Torrey[46]	All rh. manifestations	..	50	50	Girls more susceptible than boys; pericarditis and mitral stenosis more in females, polyarthritis in males
Musser[25]	.....	..	..	..	Females more susceptible at all ages; ratio of 3 to 2 in the first two decades; polyarthritis more common in men, cardiac involvement more common in women
Swift[46a]	.....	..	..	..	Polyarthritis more common in men, mitral stenosis and chorea more common in females
Hedley*					

* Since the submission of the paper an article has appeared by O. F. Hedley, (U. S. Pub. Health Rep., **55**, 1647, 1940), who has recently shown that 54% of 2539 patients with rheumatic fever admitted to Philadelphia hospitals in the years 1930–34 were females, and that 58% of 3654 patients with rheumatic heart disease admitted to the same hospitals in the same years were females.

Dieuaide[10] is instructive. Of 141 cases of rheumatic fever admitted to the Peiping Union Medical College Hospital from 1921 to 1936, he found that 88 were males; but when this figure was corrected on the basis of the sex distribution of the hospital admissions, the ratio of male to female patients with rheumatic fever was found to be 1 to 1.36. Most observers agree that in children acute rheumatic fever is commoner in the female. Thus, although DeGraff and Lingg[9] found that 56% of 1633 cases of all ages were males, when these cases were broken down into age groups, females predominated until the age of 13, the sexes were equal between 13 and 28, and there was a male predominance after the age of 28. With reference to the sex incidence in the various rheumatic manifestations, it is seen from Table 2 that polyarthritis is more common in males, while mitral stenosis, pericarditis and chorea are more frequent in females.

In summary, although polyarthritis appears to be more common in the male, the incidence of all rheumatic manifestations is greater in the female, especially in the younger age group. This is in striking contrast to the almost constant ratio of 2 males to 1 female in the reported series of patients with glomerulonephritis.

Comparison of the Preceding Clinical Infection in Acute Glomerulonephritis and Rheumatic Fever. Although the nature of the prodromal infection in acute glomerulonephritis has long been apparent, it remained for Coburn[6b] in 1931 to point out the significance of the subtle pharyngeal inflammation which precedes the bout of rheumatic fever. This inflammation is classically of a mild variety unlike the predominantly deep type of hemolytic streptococcus upper respiratory infection which precedes the onset of acute glomerulonephritis.

R. F. Loeb[18b] has summarized the experience of 9 investigators regarding the preceding infection in a total of 943 cases of acute glomerulonephritis. In general, these data show the preponderance of upper respiratory tract infections. Lyttle, *et al.*[22] have reported in detail the *type* of hemolytic streptococcus infection which preceded the onset of acute glomerulonephritis in 116 consecutive hospitalized patients, 95 of whom were under 13 years of age. Table 3 shows the prodromal clinical infection in the 104 instances where adequate data were obtained.[22]

TABLE 3.—PRODROMAL CLINICAL INFECTION IN ACUTE GLOMERULONEPHRITIS.[22]

Infection.	No. of cases.
Mastoiditis	29
Peritonsillar abscess or cervical abscess	15
Cervical lymphadenitis (moderate to severe)	11
Otitis media	8
Sinusitis	1
Acute pharyngitis (most with mild cervical lymphadenitis)	14
Scarlet fever	11
"Common cold"	8
Pneumonia (2 of 3 patients showed hemolytic streptococcus in pharynx)	3
Measles (hemolytic streptococcus in pharynx)	2
Peritonitis (organism unknown)	2
	104

It is apparent that at least 64 of these 104 reported infections can be classified as "deep" rather than "superficial." Since the publication of this series it has been our continued experience that about 2 out of every 3 patients with acute glomerulonephritis will have undergone a "deep" hemolytic streptococcus infection prior to the onset of acute glomerulonephritis.

Peters[32] has emphasized the importance of the "septic complication" in the initiation of acute glomerulonephritis. He has stressed the concept that the nephritis does not usually develop in those patients who experience an uncomplicated convalescence following scarlet fever, but rather occurs in those individuals subsequently

affected by "cervical adenitis, sinusitis, otitis media, bronchopneumonia, etc."

Additional evidence showing the importance of "deep" hemolytic streptococcus infection in the initiation of glomerulonephritis is contained in the findings of Musser, Turner and Sodeman.[26] These authors have reported 7 cases of typical acute diffuse hemorrhagic nephritis which followed postpartum sepsis. Antenatal examinations in each instance failed to reveal any evidence of renal or vascular disease. The authors state that although the streptococcus was isolated from the uterine secretions in only 1 of the 7 cases, "parametritis and endometritis, both commonly occurring postpartum without localizing signs, may have acted as deep-seated streptococcal infections in the presence of negative cervical cultures." Immunologic tests to detect hemolytic streptococcus invasion were not available.

Futcher[12] has recently reviewed the literature on the occurrence of glomerular nephritis following infections of the skin. It is apparent from the report that various authors have found that from 0 to 28% of the cases of acute glomerulonephritis in their series have followed skin infection. Futcher has added the protocols of 11 patients in whom acute hemorrhagic nephritis followed infected wounds and infections of the skin. Beta hemolytic streptococci were isolated from the cutaneous lesions of 7 of the 11 patients. In 5 of these cases beta hemolytic streptococci were also isolated from the pharynx. In 3 other instances this organism was isolated only from the pharynx.

Although the initiating agent may be similar in rheumatic fever and acute glomerulonephritis, the type of preceding clinical infection differs strikingly in these diseases. In contrast to the "deep" infections occurring prior to the onset of acute glomerulonephritis, the inflammatory process observed in rheumatic fever may be characterized as superficial, slight, or evanescent. The subtlety of the pharyngitis may be such that its detection often escapes many astute observers. Brooks and O'Regan[3] observed "catarrhal inflammatory processes" as the most frequent indication of infection prior to the onset of rheumatic fever. These authors also report that cervical or general lymphadenitis occurred in 26.7% of their series of 700 patients with rheumatic fever. The presence of otitis media, mastoiditis, peritonsillar abscess, or cervical abscess are not noted by these workers as precedents of the rheumatism. Coburn[5a] has stated that "in 100 consecutive cases of rheumatic fever developing in our group we find *none preceded by peritonsillar abscess, one preceded by otitis media, one preceded by mastoiditis, and none preceded by severe cervical lymphadenitis.*" Coburn[5c] has recently reëmphasized the importance of the mild pharyngeal infection in initiating rheumatic fever in his conclusion that "in known rheumatic subjects, suppurative lesions or highly invasive infections do not give rise to acute rheumatism."

Futcher's review and report on the importance of hemolytic streptococcus wound and skin infections in initiating glomerulonephritis has been noted above. These data are of increased interest when compared to the great rarity of such infections as prodromata in rheumatic fever.

In summary, it may be stated that whereas a "deep" hemolytic streptococcus infection precedes the onset of acute glomerulonephritis in about two-thirds of the cases, a superficial, subtle, often barely perceptible pharyngitis is the characteristic prodromal infection in rheumatic fever. It must be stated, however, that the high incidence of deep infection preceding the onset of acute glomerulonephritis may be more apparent than real since patients with severe infections are more frequently hospitalized than are those with mild infections.

Comparison of the Latent Periods Between the Infection and the Onset of Acute Glomerulonephritis, the Exacerbation in Chronic Glomerulonephritis, and the Initial and Subsequent Attacks of Rheumatic Fever. The latent period between infection and the onset of acute glomerulonephritis or exacerbation of the chronic process is difficult to determine accurately unless the patient happens to be under close medical observation during the critical period and frequent urinalyses are being done. However, in many cases the history of the development of the infection and the subsequent onset of hematuria or edema permits a reasonably accurate estimation of the length of the latent period.

Addis[1] finds equal numbers of cases of acute glomerulonephritis occurring during each of the first 3 weeks following infection, with a decreased number in the 4th week. Schick[34] and Goodall[13] find a latent period of 3 to 4 weeks for scarlatinal nephritis, with the maximum incidence falling between the 20th and 22d day. In this connection, the finding of Lyttle[21b] in scarlet fever is of interest. By means of frequent Addis counts he found that there was an explosive increase in red blood cells, leukocytes, and casts as well as an increase in proteinuria between the 8th and 45th day after the onset of scarlet fever. The modal period was about the 17th day. These urinary abnormalities were unassociated with any of the other manifestations of acute glomerulonephritis. Osman, Close and Carter[31] report that 80% of post-scarlatinal cases of acute glomerulonephritis develop between the 7th and 16th day. The same authors report a latent period of 3 days or less in only 6 of 37 cases of acute glomerulonephritis following tonsillitis, the mean being 10 days. Winkenwerder, McLæod, and Baker[48] in a series of 41 cases of acute glomerulonephritis found that only 3 occurred prior to the 4th day after the onset of the infection. The maximum incidence was 11 on the 7th day with an average of 10.9 days for the group. In 7 cases of acute glomerulonephritis following pneumococcus pneumonia[36] the latent period varied between 14 and 21 days.

The latent period between the infection and the onset of the exacerbation in chronic glomerulonephritis, however, is greatly shortened. It is almost always 3 days or less, and usually occurs within 24 hours after the onset of infection.[18,40,48] Table 4 shows the latent period of 28 exacerbations in chronic glomerulonephritis reported by Seegal, *et al.*[40] Three additional cases have been collected.

TABLE 4.—LENGTH OF LATENT PERIOD BETWEEN INFECTION AND EXACERBATION IN CHRONIC GLOMERULONEPHRITIS.

Latent period in days.	No. of exacerbations.
1	13
2	5
3	2
4	2
7	2
14	1
Unknown	6

Longcope[19c] has pointed out that "this shortening of the incubation period calls to mind the immediate or accelerated reaction following a second injection of serum." Winkenwerder, McLeod and Baker[48] have cited a case in which the latent period before acute glomerulonephritis was 13 days, whereas the latent period before a subsequent exacerbation was only 24 hours.

The initial latent (or silent) period between the onset of the infection and the first symptoms or signs of rheumatic fever is generally accepted to be from 14 to 21 days. However, there is no shortening of the latent period before the exacerbation or relapse as compared with the original attack. Coburn[5a] states, "There is a great tendency for our patients to have the same silent interval with each rheumatic attack. In 20 consecutive cases with two or more attacks there is no difference in the length of the quiescent period occurring in the first attack or in subsequent recrudescence."

The usual latent periods in acute glomerulonephritis and the exacerbations in glomerulonephritis are compared with the latent periods in the initial and subsequent attacks of rheumatic fever in Table 5. It is apparent, therefore, that there is a distinct shortening

TABLE 5.—USUAL LATENT PERIODS BETWEEN THE ONSET OF INFECTION AND THE ACUTE EPISODES OF GLOMERULONEPHRITIS OR RHEUMATIC FEVER.

Glomerulonephritis.		*Rheumatic Fever.*	
Acute nephritis	7 to 21 days	First attack	14 to 21 days
Exacerbations in chronic nephritis	1 to 4 days	Subsequent attacks	14 to 21 days

of the latent period preceding an exacerbation of nephritis as compared with that in the original attack. There is no such shortening of the latent period in rheumatic fever. It is possible that this difference is due to the disordered state of the kidney in the one

instance as compared with the temporary healed state existent in the rheumatic subject prior to the recrudescence.

Incidence of Relapse in Acute Glomerulonephritis and Rheumatic Fever. The experience of most clinicians is in agreement with the observations of Atchley and Loeb[2] and those of Lyttle[21a] with respect to the fact that patients with *healed* acute glomerulonephritis rarely undergo relapse. None of the large series of patients with *healed* acute glomerulonephritis studied by these workers were later observed to develop the chronic form of Bright's disease.

During clinical investigation of individuals with healed nephritis, bacteriologic studies by Longcope[19a] and bacteriologic and immunologic investigation by Loeb, *et al.*[16] have shown that patients with *healed* acute glomerulonephritis are extremely resistant to reactivation of the nephritis even in the face of subsequent Group A hemolytic streptococcus infection. In continuation of the study in which 8 cases were described, E. N. Loeb and her associates have observed 8 additional instances of the ineffectiveness of Group A hemolytic streptococcus infection in causing fresh nephritis in individuals in whom a previous acute glomerulonephritis was shown to have healed.

In contrast to the striking resistance of subjects with *healed* acute glomerulonephritis to subsequent attacks of acute nephritis, is the marked susceptibility of individuals with a history of rheumatic fever to repeated bouts of rheumatic fever. Mackie[23] has found that 71% of 393 patients with rheumatic fever had at least one recurrence of the acute disease. He further observed that "only 57 per cent of the first recurrences occurred within four years of the primary attack." Coburn[5a] has found that "the relapse rate in 100 rheumatic children is more than 80 per cent within five years." It is probable that the rate would be still higher if a longer period of observation were possible.

Longcope[19c] has commented on this "essential difference" between these diseases and has stated that "complete recovery from rheumatic fever, if this actually occurs, is frequently followed by subsequent acute attacks" whereas "complete recovery from acute hemorrhagic Bright's disease is rarely if ever followed by a second attack."

In summary, it is evident that relapse while a rarity following the healed state of acute glomerulonephritis is a common if not major occurrence following the rheumatic episode.

Comment. The comparison of two such different diseases as glomerulonephritis and rheumatic fever may appear to be of no moment, but from a biologic point of view such a consideration seems of interest. However dissimilar the clinical picture of glomerulonephritis and rheumatic fever, they have one important feature in common: Group A hemolytic streptococcus infection precedes the onset and the exacerbations or relapses in most cases of both diseases.

Certain biologic differences in the natural history of the two diseases have been described above. These are the geographic incidence, the sex incidence, the character of the hemolytic streptococcus infection, the shortening of the latent period in the exacerbation, and the propensity for healing and the persistence of the healed state in acute glomerulonephritis as compared with rheumatic fever. There is no explanation for these differences.

It is possible to postulate that certain strains of hemolytic streptococcus may be "nephritogenic" whereas others may be "rheumatogenic." Even if this were true, all the differences enumerated above could not be explained. In this respect, it is of interest that one of our patients with a history of chronic glomerulonephritis and rheumatic fever subsequently underwent an exacerbation of glomerulonephritis following one Group A hemolytic streptococcus infection and at a later period, a relapse of rheumatic fever following a fresh Group A hemolytic streptococcus infection. Typing of the organisms was not carried out.

The character of the hemolytic streptococcus infection, "deep" in glomerulonephritis and superficial in rheumatic fever, may in part explain the geographic variation in the incidence of the two diseases. Hemolytic streptococcus lymphangitis as a complication of filariasis is frequent in the subtropics and tropics.[24b] Glomerulonephritis secondary to infections of such a type may help to offset the decreased incidence of nephritis due to the diminished frequency of upper respiratory hemolytic streptococcus infections in the tropics as compared with the temperate zone. Attention has already been directed to the rarity of rheumatic fever following hemolytic streptococcus skin infections. As Futcher[12] has already shown, this type of prodromal infection is not uncommon in acute glomerulonephritis.

Host differences may play the definitive rôle in explaining the biologic differences under consideration. The patient who reacts to hemolytic streptococcus infection with a diffuse inflammatory process in the glomeruli is more apt to be a male than a female and is very likely to have the renal process heal. He is extremely resistant to reactivation of the nephritis once healing has been effected even in the face of subsequent hemolytic streptococcus infections. If chronic glomerulonephritis does develop, exacerbation is subject to a much foreshortened latent period after infection. In these respects nephritic man differs as a host from rheumatic man. These differences are relative, however, since there are a few reported instances of concomitant glomerulonephritis and rheumatic fever in the same individual.

Summary. A limited consideration of certain biologic differences between acute glomerulonephritis, chronic glomerulonephritis and rheumatic fever indicates that:

1. Although both diseases appear to be initiated by Group A hemolytic streptococcus infection, the geographic incidence of acute glomerulonephritis is similar for all latitude regions in North America

whereas the incidence of rheumatic fever is less frequent in the southern than in the northern latitude regions of North America.

2. Although twice as many males as females contract glomerulonephritis, this sex variation is not apparent in rheumatic fever.

3. The preceding clinical infection in acute glomerulonephritis is a "deep" hemolytic streptococcus infection in at least two-thirds of the cases, in contrast to the usual superficial pharyngitis preceding the onset of rheumatic fever.

4. There is a distinct shortening of the latent period following infection in the exacerbation of chronic nephritis as compared with that in acute glomerulonephritis. This shortening of the latent period in exacerbation or relapse is absent in rheumatic fever.

5. Relapse, while a rarity following the healed state of acute glomerulonephritis, is a common if not regular occurrence following the rheumatic episode.

We wish to thank Dr. A. R. Dochez whose point of view led to this study.

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ESOPHAGEAL OBSTRUCTION DUE TO GUMMATA OF ESOPHAGUS AND DIAPHRAGM.

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Though it is known that syphilitic lesions may occur in the esophagus, they are recognized infrequently. In the cases herein reported esophageal obstruction was produced in 1 instance by a gumma situated in the esophagus, and in 3 instances by gummatous lesions of the diaphragm. So far as we are able to determine, syphilitic disease of the diaphragm producing esophageal obstruction has not been recorded heretofore.

Gummatous lesions of the esophagus are known to be exceedingly rare.[4,6] In 1931, Guyot[2] made an extensive survey of the literature and accredited Severinus (1580–1656) with the first description of syphilis of the esophagus. Guyot collected 55 case reports of tertiary lesions of the esophagus and added 2 cases of his own. Since 1931 a few additional cases have been reported. Watson-Williams[7] in 1933 recorded 4 cases of syphilis among 350 patients with dysphagia. The diagnosis of syphilis of the esophagus seems to have been established definitely in 1 instance. The following year, Lukens and Ono[3] reported a case of tracheo-esophageal fistula. Necropsy revealed a gumma in the mediastinum involving the trachea and esophagus. Wilcox[8] reported an instance of syphilis of the esophagus in a female of 25 years. The entire esophagus was involved. Roentgenograms revealed stenosis of the lower two-fifths of the organ. This was relieved by antisyphilitic treatment. In 1936, Avery[1] recorded the case of a white male who had an obstructive esophageal lesion which responded satisfactorily to antisyphilitic

treatment and dilatation. A second patient observed by Avery presented a mid-esophageal lesion which disappeared under antisyphilitic treatment. The blood Wassermann test was negative, an unusual finding in patients with untreated visceral syphilis. The following instances of syphilitic esophageal obstruction have been observed at the Vanderbilt University Hospital during the past 15 years.

Case Reports. CASE 1.—E. S., white female aged 48, was admitted to the Out-Patient Department on December 30, 1936, because of difficulty in swallowing during the preceding 3 months. She felt that the site of obstruction was under the upper end of the sternum. Regurgitation of solid foods occurred occasionally at first and gradually increased in frequency. For several weeks before admission she experienced difficulty in retaining liquids. Loss of weight and strength ensued. The patient's husband had died of general paresis at Vanderbilt University Hospital 1 year before her admission.

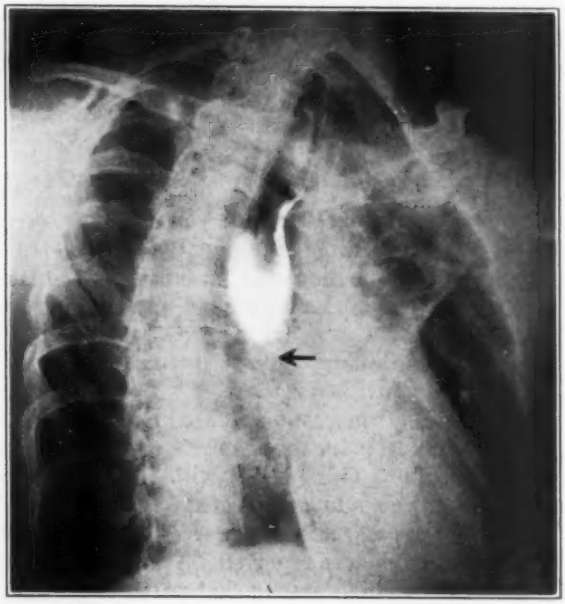

FIG. 1.—Case 1. Esophageal obstruction. Arrow indicates the site with dilatation above this point.

Physical Examination. The patient appeared chronically ill, and except for malnutrition and marked weakness the general physical examination was not remarkable.

Special Examinations. The Wassermann and Kahn tests on the blood were positive. The cerebrospinal fluid was normal.

Roentgenologic examination of the esophagus revealed "almost complete obstruction at about the mid-point of the esophagus with an irregular canalization through the area of obstruction suggesting carcinoma" (Fig. 1).

Esophagoscopy on January 5, 1937, by Dr. Guy Maness, revealed a constriction at about the mid-point of the esophagus. A band of scar tissue was observed in this area, below which there was a granular tumor. The appear-

ance of the latter was suggestive of carcinoma. Microscopic examination of biopsy tissue revealed a chronic inflammatory reaction with no evidence of neoplastic disease.

Course. Beginning January 8, 1937, she was given bismuth salicylate intramuscularly at weekly intervals and potassium iodide thrice daily. After 2 weeks swallowing definitely improved, and after the 4th week of treatment, the taking of food caused very little trouble. On March 5, 1937, after 7 injections of bismuth and 1 of neoarsphenamine, the patient was entirely free of symptoms. A Roentgen ray examination on this date showed an irregular narrowing of the esophagus with some delay in the passage of barium. However, marked improvement since the last examination was apparent. Continuous antisyphilitic treatment was given until she had received 66 injections of bismuth and 50 injections of neoarsphenamine. She gained 25 pounds in weight and was greatly improved. The blood Wassermann and Kahn tests remained positive.

FIG. 2.—Case 1. Slight constriction due to scar is present 2½ years after the institution of antisyphilitic treatment.

Esophagoscopy on June 2, 1937, indicated an increase in the degree of constriction, and consequently dilatation was performed. Subsequently the stricture was dilated 22 times. At the last 7 treatments a No. 45 F olive bougie was easily passed. On December 24, 1937, a Roentgen ray examination showed less obstruction and less dilatation above the point of obstruction than had been observed previously. In May, 1939, a Roentgen ray examination revealed only a slight stricture at the site of the previous obstruction, and a small traction diverticulum (Fig. 2). The patient was last seen in May, 1940, at which time she was entirely free of symptoms.

CASE 2.—J. K., a colored male aged 69, entered Vanderbilt University Hospital November 20, 1925, because of breathlessness, difficulty in swallowing and pain in the abdomen and flanks. These symptoms began about 1 year before admission, their sequence being pain in the region of kidneys, dyspnea on exertion, cough, difficulty in swallowing and abdominal pain after meals. Finally, a short time before admission to the hospital, the patient became bedridden because of weakness. He had lost 45 pounds in weight during the year.

The past history revealed little of interest except that the patient had acquired syphilis at the age of 49.

FIG. 3.—Case 2. Esophageal obstruction at the level of the diaphragm.

Physical Examination. He appeared chronically ill. Dyspnea and orthopnea were present. The veins on the right side of the neck were more prominent than on the left. Substernal dulness was increased but the heart was apparently not enlarged. A systolic murmur was heard over the precordium and over the aortic area. Retraction of the chest wall together with dulness on percussion and distant breath sounds were noted over the region of the upper lobe of the right lung.

Special Examinations. The Wassermann test on the blood was positive. Roentgenologic examination showed fibroid tuberculosis of the lungs. A barium meal was markedly delayed in its passage through the terminal portion of the esophagus. There was moderate dilatation of the esophagus above the lesion, which was thought to be a carcinoma (Fig. 3).

Course. Deep Roentgen ray treatment was given. Within a week regurgitation of food was less troublesome and by December 11, 1925, a

Roentgen ray examination revealed free passage of barium from the esophagus into the stomach. The patient was discharged from the hospital considerably improved. Two months later he was readmitted because of recurrence of dysphagia which began a week after discharge. Dyspnea and orthopnea were marked and he again complained of pain in the kidney regions. The lower anterior portion of the chest was also the site of vague discomfort.

The physical examination on the second admission revealed no new findings. Five days after his second admission to the hospital, he became comatose, and died on the following day.

The clinical diagnoses were carcinoma of the esophagus, fibroid tuberculosis of the lungs, latent syphilis, and bronchopneumonia.

Autopsy. The findings of chief interest were related to the esophagus and were described by the pathologist as follows: "The esophagus is so compressed where it comes through the diaphragm that the lumen is practically closed. The mucosa in this region is white, thickened, almost bloodless, and is thrown into longitudinal furrows which, when the structure is opened, tend to push out into the incision. The muscular coats of the esophagus are also thickened. However, there is no evidence of either inflammation or neoplastic disease of the esophagus. There is simply a constriction of the lumen. The latter is caused by a hard tumor mass in the diaphragm which almost completely encircles the esophagus. A careful dissection reveals that this mass involves the medial portion of the diaphragm including the pillars and the upper medial portion of the liver. The tumor measures approximately 5 x 5 x 6 cm. in size and is nodular. The diaphragmatic muscle surrounding the tumor is markedly fibrosed. Posteriorly the mass extends to the bodies of the first and second lumbar vertebræ, from which it is removed with some difficulty. It extends downward about 1 cm. into the substance of the liver. A sagittal section of the mass reveals a large, irregular, orange-yellow, necrotic fibrous focus about 4 x 5 x 6 cm. in size, which is surrounded by a bluish-white, gristle-like capsule about 1 cm. in thickness. There is no evidence of malignant neoplasm. The entire mass appears to be fibrous tissue with a caseous, necrotic center."

Microscopic examination of the mass revealed chronic inflammatory reaction with caseous necrosis, epithelial cells and fibroblasts. There were occasional foreign-body giant cells. These findings were present both in the portion of the mass attached to the liver and in the portion from the diaphragm proper.

The anatomic diagnosis was "gumma of liver and diaphragm obstructing the esophagus." Additional diagnoses were adhesive pleuritis, fibrosis of the right lung, dilatation of the aortic arch, arteriosclerosis, and focal sclerosis of the myocardium.

Case 3.—S. S., a colored male aged 56, entered Vanderbilt University Hospital on December 10, 1928, because of the regurgitation of solid food. He stated that for 6 weeks he had noted that solid food would pass "about half-way down" and then would be promptly regurgitated. He had no pain and his appetite had remained good. He had lost about 30 pounds in weight during the present illness.

The past history was essentially negative.

Physical Examination. Nothing remarkable was noted except evidence of recent loss in weight

Special Examinations. The Wassermann reaction on the blood was positive. A roentgenologic examination with barium revealed an obstruction at the lower end of the esophagus. Marked dilatation of the esophagus was present above the obstruction. The roentgenologist interpreted the findings as being due probably to esophageal spasm.

Esophagoscopy was unsuccessful due to the patient's struggling. Several

hours later a crepitant swelling appeared in the neck. Operation revealed a small tear in the esophagus which was closed without difficulty.

On December 15, 1928, the abdomen was opened. The stomach was markedly atrophic. It was opened in order to facilitate exploration of the lower end of the esophagus. The latter was found to be compressed by a tumor mass in the diaphragm. The mass, which felt smooth and "distinctly doughy," lay to the right of the esophagus and was in intimate contact with the aorta. In view of the positive Wassermann test it was thought that the tumor probably represented a gumma of the diaphragm.

During the first 2 weeks following operation he was fed through a gastrostomy tube and was given 4 injections of neoarsphenamine with the development of a mild arsenical dermatitis. He recovered promptly, and on removal of the gastrostomy tube was able to eat quite satisfactorily. A Roentgen ray examination on January 20, 1929, revealed a "slight constriction, but no obstruction at the lower end of the esophagus." Marked dilatation of the esophagus was still present. He was discharged a week later. On March 11, he returned to the clinic because of the return of dysphagia a few days before. Three injections of bismuth intramuscularly and iodides had been given by his family physician. Dilatation of the esophagus was attempted twice. Only small dilators would pass the obstruction. He returned to the clinic after an absence of 5 weeks. He was entirely free of symptoms and had gained 20 pounds in weight since March 11. A fluoroscopic examination revealed no esophageal obstruction. He was last seen June 18, 1929, after having completed a course of 8 injections of bismuth administered by a private physician. He stated that he felt perfectly well and he experienced no symptoms of esophageal obstruction.

Further information was obtained from the patient's wife in July, 1939. He had died in April, 1937 (8 years after his last visit to the clinic), without receiving further antisyphilitic treatment and without return of dysphagia. Although the exact cause of death could not be ascertained, certainly it was unrelated to the esophagus, since it was stated that he died 2 weeks after an operation for an ulcer of the foot.

Case 4.—H. C., colored male aged 24, was admitted to the Vanderbilt University Hospital clinic on January 10, 1934, because of difficulty in swallowing of 3 months' duration. At times food would "seem to stop" at the end of the ensiform cartilage and on occasions it would be regurgitated. He had lost approximately 20 pounds in weight.

The past history revealed that he had had a lesion on the penis in 1927 which was treated by 3 intravenous injections.

Physical Examination. Except for evidence of recent loss of weight, there was nothing remarkable.

Special Examinations. Repeated Wassermann and Kahn tests on the blood were positive.

A roentgenologic examination on January 11, 1934, revealed almost complete obstruction at the lower end of the esophagus. The roentgenologist pointed out that the filling defect was rather smooth and suggested that it was due possibly to a gumma (Fig. 4). Esophagoscopy by Dr. Maness revealed marked symmetrical narrowing of the lumen at the line of the diaphragm. There was no ulceration. The mucosa was pale but no scars were seen. It was concluded that the obstruction was due to an extrinsic lesion.

Course. A provisional diagnosis of gummatous syphilis of the diaphragm was made. The patient received 9 injections of bismuth salicylate and 4 injections of neoarsphenamine during the next 8 weeks. Although he then swallowed liquid food without difficulty and gained 20 pounds in weight, solid food continued to produce symptoms and a roentgenologic examination

April 7 was interpreted as indicating almost complete obstruction of the lower end of the esophagus. Attempts at esophagoscopy on April 7 and 14 were unsatisfactory because he coöperated poorly. A silk string was passed for the purpose of subsequently dilating the stricture with a Plummer bag. His temperature rose to 100.8°, he complained of pain in the xiphoid region, and dysphagia increased. Therefore the procedure was discontinued.

On May 16 esophagoscopic examination was repeated. A cicatricial stenosis of the esophagus was encountered at the level of the diaphragm. The mucous membrane was very pale and showed definite scarring. It was impossible to pass flexible bougies completely into the stomach due to resistance of the stricture. To the operator the sensation was that of stricture rather than muscle spasm.

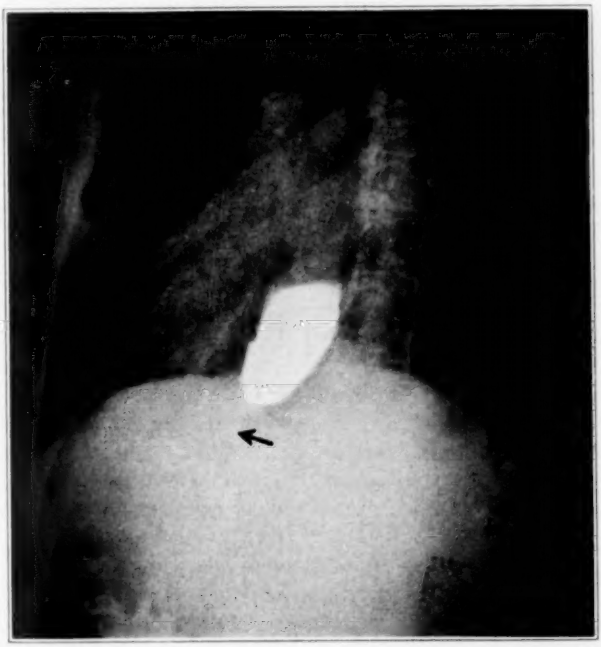

FIG. 4.—Case 4. Esophageal obstruction. The arrow points to the site of obstruction at the diaphragmatic level.

Two weeks later a gastrostomy was performed. Subsequently retrograde dilatation of the stricture was accomplished by bougies inserted through the stomach along a silk string. He was fed through the gastrostomy opening. Antisyphilitic treatment was continued.

On June 26 a No. 22 F. bougie passed the stricture. Treatments were continued and a month later it was possible to pass a No. 40 F. bougie, inserted from above, past the stricture. The passage of bougies of this size was continued at intervals during the remainder of the year. The gastrostomy wound closed satisfactorily.

The patient was seen last on August 20, 1935. During the preceding 14 months he had received 15 injections of neoarsphenamine and 28 injec-

tions of bismuth. In the autumn of 1939 a member of his family stated that he was in excellent health, entirely free of symptoms, and was working in an adjacent state.

Discussion. That esophageal obstruction may occur as the result of gummatous syphilis has been illustrated by the 4 cases herein reported. In 1 instance the tertiary lesion of syphilis was limited to the esophageal wall, whereas in the remaining 3 cases the obstruction was due to gummatous involvement of the diaphragm at or near the esophageal hiatus.

The differentiation of gummatous lesions of the esophagus or diaphragm from obstruction due to carcinoma or cardiospasm can only be made by direct examination (esophagoscopy and biopsy), and the ultimate response to treatment. Antisyphilitic treatment for gummatous lesions producing esophageal obstruction may not only fail to relieve but may actually increase the obstruction ("therapeutic paradox"). Because of resultant fibrosis and contraction of scar tissue esophageal dilatation will probably be necessary.

Case 2 illustrates the importance of accurate diagnosis in esophageal obstruction. The age of the patient and the results of roentgenologic examination led to the diagnosis of carcinoma, and the use of palliative treatment in spite of the fact that he was known to have syphilis. Appropriate treatment at the time the patient was first seen probably would have relieved the obstruction.

Finally it should be emphasized that esophageal obstruction in a case of chronic syphilis may be carcinomatous. Gummatous lesions of the esophagus or diaphragm are rare. Indeed, in individuals with syphilis, the incidence of carcinoma of the esophagus may be greater than obstructive gummatous lesions. This probability has been discussed by Touraine.[5] Nevertheless, the importance of accurate diagnosis and appropriate treatment is apparent in the light of Case 2.

Summary. Four cases of esophageal obstruction due to gummatous lesions of syphilis have been reported. In 1 case the obstruction was due to a gumma of the esophagus. Gummata of the diaphragm producing esophageal obstruction were present in the remainder. In 3 instances the nature of the lesion was recognized and antisyphilitic treatment and active dilatation of the obstruction offered relief. In 1 case, erroneously diagnosed carcinoma of the esophagus, the patient died without benefit of appropriate treatment.

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SHORT WAVE DIATHERMY IN CHRONIC PROSTATITIS.

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THE frequent reappearance of a patient with prostatitis in the office of the urologist emphasizes the chronicity of the disease and the palliative effect of treatment for this irksome condition. Heat has been of great value to such patients and the opinions of physicians vary as to the method of application. The investigations of Coulter and Osborne[2a] and Coulter and Carter,[1] show that the electromagnetic field is the most efficient and comfortable method of securing heat in the deeper tissues of the body. We, therefore, decided to investigate the effectiveness of this heating method in the treatment of prostatitis. In addition it was decided to investigate the temperature of the prostate before and after the heat treatment.

In an experimental study on dogs, Schmidt, Beazell and Ivy,[11] found that short wave diathermy increased the blood flow of the intestine and colon. Because of the rich blood supply of the prostate it is obviously impossible to perform a satisfactory study of the circulation of that organ. Coulter and Osborne,[2b] in their study of pelvic heating, found temperatures higher than those procured by other methods. Titus[13] believes that short wave diathermy is less effective in concentrating energy to the prostate than conventional diathermy. Simpson and Kendell[12] report in a paper on the treatment of gonococcal infection other than arthritis, "Among patients with chronic prostatitis and its complications, 88.8% of the first treated were cured while only 31.5% of the patients in the control group were cured." Elkin and Krusen[3] have reported that 2 patients suffering with prostatic abscesses secured a clinical remission when heat localized to the rectum and fever hterapy was used in combination.

Methods. Eighty-five patients were diagnosed as chronic prostatitis and were given treatment. The patients varied from 18 to 61 years of age and were divided into 4 groups as shown in Table 1. Grouping of these patients was undertaken so that both duration of the treatment as well as its intensity could be varied. A previous experience had shown us that best results were obtained in these groupings.[5]

Each patient received a genital examination and the urethra was calibrated. A 2-glass urine examination was made; the prostate digitally examined, prostatic secretion expressed and examined for pus and lecithin content, thus establishing the status of the disease.

Treatment was given by means of a pancake coil, enclosed in a bakelite disk and placed underneath the seat of a wooden chair. The disk was connected to an inductotherm. The patient with the necessary clothing

removed sat on the seat of the chair in the usual manner, and the machine setting was placed at a point which we had previously found to give the best clinical results and to produce maximum temperature rise. Each treatment was given for a period of either 20 or 30 minutes as shown in Table 1. Each patient received an average of 10 treatments.

TABLE 1.—DATA ON PATIENTS TREATED.

Group.	No. of patients.	Treatment time (min.).	Age range (years).	Machine setting.
1	26	30	21–56	80
2	24	20	18–61	90
3	17	20	28–52	80
4	18	30	22–58	90

When the patient's treatment was terminated he was instructed to report for reëxamination at 3 weeks' and 3 months' intervals when the same procedure of evaluation, just described, was followed.

Posterior urethral temperatures were taken before and after treatment. A special thermocouple made for this purpose was passed to the posterior urethra. Potential differences were read by means of a Leeds & Northrup potentiometer. The thermocouple was calibrated against a standard thermometer and found to have a standard error of plus or minus 0.04° F.

Results. The results of treatment in pus content of the prostatic secretion is shown in Table 2.

TABLE 2.—RESULTS OF TREATMENT ON THE PUS CONTENT OF PROSTATIC SECRETION.

Group.	Before.	After.	Subsequent examinations.	
			Six weeks.	Three months.
1	10–80% Av. 44.1%	24 decreased to 14.9% 2 increased to 80–90%	6 decreased to 5% 1 increased to 40%	3 decreased to 5% 1 increased to 40%
2	10–25% Av. 17.5%	13 decreased to 15% 14 unchanged 6 increased to 30% 1 developed epididymitis	2 decreased to 5%	2 decreased to 5%
3	5–90%	8 decreased 10–70% 1 burn 1 gonorrhea 3 increased 1 fibrous prostatitis unchanged 3 unchanged	5 decreases remained 10–70%	3 decreases remained 10–70%
4	5–90%	15 decreased 5–35% 2 increased 1 unchanged	7 decreases held 2 increased	4 decreases held 1 increase held

Before treatment the pus content of Group 1 varied from 10 to 80% with an average of 44.1%. Under treatment, the pus content of 2 patients was increased from 80 to 90%, but the remainder were reduced at the end of treatment to 14.9%. There was an average rise of 0.6° F. in oral temperature but no appreciable rise in the number of white blood cells. A check in 6 cases was obtained at 6 weeks and 3 cases at 3 months after treatment. In 5 instances the pus content remained at 5%, or lower, while 1 increased to 40% at 3 months. Examination of 1 individual who showed a rise from 80

to 90% revealed a markedly infected maxillary sinus from a cavity of a tooth which had penetrated the sinus. The case which rose to 40% was markedly improved by foreign protein injection (peptone) but returned again to 40% after a course of massage.

Twenty-four cases were treated in Group 2 for 20 minutes at a machine setting of 90, and each patient received an average of 12 treatments. The urinary symptoms, discharge, pain in the back and perineal pain, complained of by this group, were improved or cured in 11 of these patients, while 1 was unchanged. Two urines were cloudy in both glasses, the remainder "clear with shreds and clear." In 1 patient there was no change. Expressed prostatic secretion before treatment varied from 10 to 25% with an average of 17.5%. The white blood cell count of 3 patients was over 10,000, and treatment did not change it. There was an average rise of 0.3° F. in oral temperature and it was noted that men over 40 years showed the highest rise in oral temperature regardless of pus content of the prostate. After treatment 2 patients showed an increase of 30% and 9 patients showed a decrease of 15% in pus content; 1 patient developed an epididymitis. Symptomatically 10 patients were cured or improved and in 1 case there was no change. Six weeks and 3 months checks obtained on 2 patients revealed a less than 5% pus content. One 38-year-old man with an enlarged and tender prostate, arthritic symptoms, premature ejaculations, but with only about a 5% pus content received complete relief; another with no physical findings and only a 10% pus content developed an epididymitis.

In Group 3 treatment was given for 20 minutes with a machine setting at 80. They complained of urinary symptoms, premature ejaculation, backache and of perineal pain. The urine of all was "clear with shreds and clear;" and 5 patients had a white blood cell count of over 10,000. The average oral temperature change in this group was 0.8° F. and the pus content of expressed secretion varied from 5 to 90%. These men received an average of 11 treatments, the longest 14, while 3 patients received 4, 5 and 6 treatments. One of the last 3 patients contracted gonorrhea, 1 had a fibrous prostatitis and when his symptoms were relieved refused further treatment, and the last patient developed a minor burn. Two other patients were considered to have a fibrous rather than a follicular prostatitis. Of the 14 patients who received 10 to 14 treatments, 8 had their pus contents reduced from 70 to 10% in each case. Three were increased and 3 remained unchanged. Another check of 6 patients made 6 weeks later revealed no further pus increase in 5 of the 6 patients examined. Another later check of 3 of these 6 patients showed no further increase.

Eighteen patients were treated in Group 4 for 30 minutes at an intensity setting of 90. They complained of urinary symptoms, of discharge, of sexual symptoms, of back pain and of perineal pain. Four

urines were "cloudy, cloudy"; 1 "cloudy, hazy," and the remainder "clear with shreds and clear." Five patients were found to have white blood cell counts of over 10,000 while the average rise in oral temperature was 0.5° F. The pus content of expressed secretion varied between 5 and 50%. Two patients demonstrated an increase of pus cells under treatment, 1 remained stationary and 15 were decreased from 5 to 35%. A 6 weeks' check of 9 patients showed 2 to have increased while 7 had maintained their decrease. Of 5 patients reporting for reëxamination after 3 months, 4 had maintained their decrease while 1 still showed an increase. One patient developed an epididymitis after 6 treatments, 1 felt fine and dropped out after 5 treatments, while 1 dropped out after 8 treatments. The remainder received from 12 to 15 treatments.

A survey of the entire series of patients revealed that all but 2 so afflicted received relief from their sexual symptoms, 3 noted improvement in their sexual powers. With the exception of 5 patients there was an early response to treatment with moderate to complete relief of all subjective symptoms. The more resistant cases exhibited a moderate exacerbation of subjective symptoms, in part verified by slight fever and leukocytosis which continued into the 5th week of treatment, at which time there was a marked improvement as determined by complete remission of subjective complaints, reduced leukocyte count, lowered temperature, and general appearance of well being. At the end of the series of treatment these patients showed a definitely reduced pus content of expressed secretion and on subsequent reëxamination showed a continued small amount of pus cells with increased lecithin content.

Burns have been known to occur when using the electromagnetic field, and unfortunately, we experienced 2; 1 superficial and the other a third degree burn in the region of the buttocks.

In Table 3 are shown the results of 37 posterior urethral tempera-

Table 3.—Posterior Urethral Temperature Before and After Treatment by Inductotherm (Temp. ° F.).

Before.	After.	Before.	After.	Before.	After.
99.2	102.7	99.8	102.3	98.4	101.4
99.7	98.7	100.4	101.9	98.5	103.9
98.4	99.5	99.8	100.8	98.0	100.9
98.6	99.8	100.3	102.0	97.5	100.1
98.6	101.1	99.4	100.2	98.5	100.0
99.2	100.0	99.0	100.1	98.7	100.5
98.2	100.3	99.1	102.0	97.7	99.6
98.5	100.6	100.3	100.6	98.0	101.4
98.8	100.0	99.5	101.5	99.3	101.8
98.8	100.6	99.5	101.2	98.1	99.4
100.5	101.6	99.0	100.9	98.8	100.9
100.3	101.0	99.2	103.0	97.6	100.4
				98.6	101.0
			Total average	98.9	100.9
				± 0.14	0.17
			Temperature rise	2.0° F.	

tures when using electromagnetic induction. Table 4 gives temperature readings of 6 patients using the Elliott machine applied directly to the prostate and Table 5 gives the temperature rise

TABLE 4.—POSTERIOR URETHRAL TEMPERATURES BEFORE AND AFTER TREATMENT WITH ELLIOTT MACHINE (TEMP. ° F.).

Before.	After.
98.1	99.3
97.5	97.9
97.9	98.3
97.8	98.4
98.4	98.8
98.9	99.1
Average 98.1	98.6
± 0.22	0.24
Temperature rise . . .	0.5° F.

TABLE 5.—POSTERIOR URETHRAL TEMPERATURE BEFORE AND AFTER TREATMENT BY CONVENTIONAL DIATHERMY.

Before.	After.
97.8	104.4
98.0	105.4
98.4	104.7
98.0	102.6
98.8	102.7
99.2	102.8
98.7	104.2
99.1	102.2
99.6	104.1
Average 98.6	103.7
$\sigma \pm$ 0.2	$\sigma \pm$ 0.37
Temperature rise . . .	5.1° F.

secured by means of conventional diathermy applied locally and directly to the prostate by means of a prostatic electrode. Table 6 gives a comparison of three methods, the standard error difference,

TABLE 6.—COMPARATIVE TEMPERATURE MEASUREMENTS IN THE POSTERIOR URETHRA USING VARIOUS HEATING METHODS.

Method.	Treat. time, min.	Temperature, ° F.				Temp. diff.		No. of observ.
		Before.	$\sigma \pm$.	After.	$\sigma \pm$.	Actual.	Diff. $2\sigma \pm$.	
Elliott machine	45	98.1	.22	98.6	.24	0.5	0.64	6
Convent. diathermy	20	98.6	.20	103.7	.37	5.1	0.84	9
Inductotherm	20–30	98.9	.14	100.9	.17	2.0	0.44	37
Control	45	97.6		98.4		0.8		1

and whether or not the differences found were statistically significant. A control was run for a period of 45 minutes. It can be seen by referring to Table 6 that there was no significant rise in tem-

perature when the Elliott machine was used although 45 minutes was given to each treatment. Conventional diathermy localized to the prostate showed the most marked average increase of 5.1° F. The temperature rise secured by the inductotherm averaged 2.0° F.

Discussion. As a result of our investigation it is our impression that inductotherapy is very effective in reducing the subjective symptoms of chronic prostatitis. A majority of the cases revealed a lowered pus cell count in expressed secretion but, unfortunately, we were unable to follow these cases long enough to draw a fair comparison with mechanically accomplished drainage. It is interesting to note that there was no significant temperature rise in the prostatic urethra when the Elliott machine was used, and inasmuch as several reports[9, 10] appeared attesting to its value in the treatment of prostatitis, the question naturally arises as to whether a temperature rise is essential in securing the necessary therapeutic results. That a temperature rise is essential to secure the maximum vasodilatation and blood flow is the most prevalent opinion of the day although this has never been fully established. Johnson, Scupham and Osborne[6] have shown that there is apparently an optimum temperature for the maximum blood volume change and once this temperature is exceeded there is apparently a decrease in the blood flowing to the part.

Herring,[4] using conventional diathermy, reported a prostatic urethral temperature of 106° F. and 0.5° F. when using the Elliott machine. He claims that a temperature of the tissues is necessary for a therapeutic result, and that the temperature should range from 105° F. to 106° F.

Mikel and Taube[8] attributed their successful results secured when using the Elliott machine to the fact that a much greater dosage of heat was possible. They stated it was a more efficient means of applying heat because known temperatures could be maintained. Other methods, they stated, lacked constancy of temperature and control of heat.

Likewise, Lewis[7] states that the immediate effect of the Elliott machine treatment is a localized pelvic hyperemia and a local elevation of temperature. It would appear from our temperature studies that success of the Elliott treatment cannot be attributed to an increased temperature, and it may well be that an increment of heat is not essential. An increased hyperemia could readily occur as a result of the treatment and this may explain the therapeutic results secured.

Conclusions. 1. Eighty-five patients suffering with chronic prostatitis were each given an average of 10 inductothermy treatments.

2. Inductothermy was effective in reducing the subjective symptoms of chronic prostatitis.

3. Objective findings were improved in a majority of the cases.

4. Posterior urethral temperatures were taken by means of

thermocouples. An average rise of 2° F. was obtained when using the electromagnetic field.

5. The highest posterior urethral temperature was obtained by means of conventional diathermy. There was no significant temperature rise when the Elliott hot-water treatment was given.

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HEAD RETRACTION REFLEX.

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When pyramidal signs, that is, signs of an affection of the upper motor neuron, are found, the next step in examination is to determine the location of the lesion in the long course of the pyramidal corticospinal tracts. The pyramidal signs themselves usually do not give any reliable clue to that end. The Babinski sign, for instance, is exactly the same whether the lesion lies in the dorsal spinal cord or in the cortex. However, the history of the case and the motor, sensory and psychic phenomena associated with the disturbance are helpful in localizing the lesion. The problem before us is: how much can we learn regarding the location of the lesion from the behavior of the reflexes alone? This problem arises especially in cases in which the pyramidal tracts are exclusively or predominantly affected, and in which the other tracts and systems are left more or less intact.

The purpose of this article is to draw attention to a reflex which indicates that if a bilateral lesion of the pyramidal tract is present, it is not in the spinal cord but must lie above the upper cervical cord, that is, in or above the brain-stem.

In examining a patient with bilateral pyramidal signs, it is advisable to start with the lower extremities and to proceed upward in an effort to find the highest level at which these signs can still be elicited. The level immediately above this point indicates the location of the lesion. A positive Babinski on both sides indicates that the lesion must lie above the third or fourth lumbar segment.

Marked exaggeration of the knee and adductor jerks with patellar clonus indicates a lesion above the lumbar enlargement. In the area of the trunk, the level of the lesion may be determined from the behavior of the reflexes of the abdominal wall. The neurologic textbooks use chiefly the term, "abdominal reflex,"* and designate it as a "superficial reflex" which consists of contraction of the abdominal muscles with deviation of the umbilicus as a reaction to stroking the skin of the abdomen with a pin, a pinwheel or a similar object. Loss of this abdominal reflex is regarded as an early pyramidal sign and indicates that the lesion lies above D6. This reflex would be more appropriately called an "abdominal *skin* reflex," in contradistinction to the deep reflex of the abdominal muscles which should be called "abdominal *muscle* reflex." In the latter, as in all so-called deep or tendon reflexes, a sudden passive stretching of the muscles themselves provokes their contraction.

The sudden stretching of the abdominal muscles may be brought about by various means. The examiner may place his hand, palm downward, flatly on the patient's abdomen, and tap the dorsum of this hand with a percussion hammer. Or a ruler or muscle plessimeter (such as that devised by Troemner,[5] which consists of a bayonet-shaped blade and is made of celluloid), may be placed on the abdomen and tapped briskly. The edges of the lower thoracic aperture, the symphysis ossis pubis, the abdominal muscles on the flanks, or other points may be tapped. The best method for eliciting a bilateral abdominal muscle reflex is to place either a limb of the muscle plessimeter or the hand of the examiner obliquely in the middle of the abdomen beneath the umbilicus and to press down so as to stretch the muscles. Tapping the plessimeter or hand with the reflex hammer in a downward direction provokes an additional, brisk stretching of the abdominal muscles and brings forth a massive contraction. This contraction is due to the hypertonicity released by pyramidal involvement. The reflex reaction is often intense and may be accompanied by a reflexive adduction of the legs and, although less frequently, also of the arms. In the presence of pyramidal signs of the lower extremities, loss of both the abdominal skin and the abdominal muscle reflexes indicates a lesion in the dorsal part of the spinal cord below D6. Loss of abdominal skin and exaggeration of abdominal muscle reflex indicates a pyramidal lesion above D6.

Thus, in high situated bilateral pyramidal involvement two pyramidal abdominal signs are observed, namely, loss of the abdominal skin reflex and exaggeration of the abdominal muscle reflex. The exaggeration of the abdominal muscle reflex, which is weak in a normal person, apparently constitutes a more delicate pyramidal sign than the loss of the abdominal skin reflex. I have seen patients

* In his fundamental work on "Neurology" (1940), S. A. K. Wilson[7] refers throughout to the "Abdominals." R. Brain, in the second edition of his textbook on "Nervous Diseases" (1940), uses the same expression.

with definite bilateral involvement of the pyramidal tract in whom the abdominal muscle reflexes were exaggerated although the abdominal skin reflexes were preserved.

No detailed discussion will be given here on the diagnostically important and fascinating study of the dissociation of the reflexes of the fingers, hands and arms. Suffice it to say that exaggeration of the reflexes and pyramidal signs of the fingers, associated with exaggeration of the triceps reflex and loss of biceps and radial reflexes, clearly indicate a lesion in C5. On the other hand, spastic phenomena of the fingers associated with preservation or exaggeration of the biceps and radial reflexes and loss of the triceps reflex, indicate a lesion in C6–C7. If bilateral spastic phenomena are present throughout the whole arm, the lesion must lie above C5.

Considerable difficulty in topical diagnosis is encountered when, in the presence of a spastic tetraplegia, it must be decided whether the lesion lies in the upper cervical cord, in the brain-stem, or in the brain itself. This difficulty arises because, especially in slight lesions, the pyramidal signs in the area of the neck and face are few and unreliable. The famous Magnus-de Kleijn's neck reflexes, although valuable physiologically, are here seldom of diagnostic significance.

In the area of the face the jaw jerk, which is a purely trigeminal reflex, is usually examined first. Marked exaggeration of this reflex, eventually associated with clonus or trismus, indicates a lesion of the corticopontine tracts above the motor fifth nucleus. It is sometimes difficult to judge whether or not this reflex is exaggerated and it is still harder to draw any definite conclusions from such an exaggeration. This reflex usually is markedly exaggerated in pseudobulbar palsy, but other signs and symptoms of lesions of the corticobulbar tracts are here so apparent that they completely overshadow the exaggeration of the jaw jerk.

In a lesion of the corticopontine tracts of the trigeminus, a positive corneomandibular reflex which consists of a contralateral movement of the lower jaw in a horizontal plane, is occasionally found after pressure has been exerted on one cornea. I have seen this reflex pronounced in amyotrophic lateral sclerosis and in a diffuse pontine lesion, but since it is not always present when it might be expected and is not constant in the same patient, it is of little value in diagnosis.

The much neglected "snout" reflex is useful for the detection of a corticobulbar lesion. On slight tapping of the middle of the upper lip with a percussion hammer, the lips briskly protrude to form a snout. This reflex occurs normally in the newborn during the first days of life. It is often pronounced in severe diffuse brain lesions and in lesions of the cortex and of the corticobulbar tracts, such as encephalomalacia, hydrocephalus, progressive paralysis, pseudobulbar palsy, senile dementia, chronic alcoholism, and other organic

psychoses. Opinions differ as to the significance of this reflex, and its exaggeration is not easily evaluated. However, I am under the impression that a greatly increased snout reflex does indicate to some degree the involvement of the corticobulbar pathways.

Once, on examining a patient with amyotrophic lateral sclerosis for this snout reflex by tapping the middle of the upper lip with a percussion hammer, I observed that this reflex was not pronounced but that every time the upper lip was struck with the hammer, a reflex movement, consisting of a brisk, quick, involuntary backward jerk of the head, took place. This movement occurred even when the patient lay on his stomach with the head hanging freely over the edge of the table. In this position the reflexive retraction took place against the weight of the head. A careful analysis of this reflex showed that the muscles in the nape of the neck retracted the head; in other words, this was a true *head retraction reflex*. As is the case in all so-called deep or tendon reflexes, this retraction of the head always follows a quick stretching of the muscles. The stretching of these muscles takes place when the tap of the hammer on the jaw provokes a sudden bending of the head to which head retraction is a reflexive answer. The muscles in the nape of the neck respond to stretching with a reflexive contraction in the same way as the quadriceps muscle does when it is longitudinally stretched by a blow on the patellar tendon.

The head retraction reflex may be elicited in different ways all of which cause a sudden bending of the head. The root of the nose may be tapped with the percussion hammer in a downward direction, or the middle of the upper lip may be tapped; or the patient may clench his teeth tightly and be given a tap on the chin downward. The reflex may sometimes be elicited by tapping the middle of the occipital bone upward and forward. However, the best method appears to be the tapping of the upper lip. The intensity of the reflexive response depends on the force of the tap, its direction, and the length of the lever on which the blow acts to cause the rotation of the head through a transverse axis. The reflex is most difficult to elicit by striking the nape of the neck upward because the lever on which the blow acts to bring about a bending of the head is too short.

The best way to observe the reflexive movement of the head is to sit beside the patient at his right side while the light is on his left. For the elicitation of the head retraction reflex, as for that of the other deep reflexes, all the muscles concerned must be relaxed. At first this may be difficult to achieve, and it is astonishing to see how tensely many patients hold their neck muscles. In an examination for the presence of the head retraction reflex, all the different maneuvers for the reinforcement of the knee jerk may be applied: the maneuver of Jendrassik may be used; the patient may be instructed to grasp the arm of the examiner, to squeeze his own

thighs, to cough, to take a deep breath, to gaze at one point; or other means of diverting his attention may be employed. On the other hand, some degree of tension of the head retractors is favorable for the appearance of this reflex. It is, therefore, essential before eliciting the reflex to ask the patient to keep his head bent forward slightly and loosely, or even to make a very slight movement of the head backward.

The head retraction reflex has never been found strongly positive in normal persons even though other tendon reflexes were exaggerated. Nor has it been found positive in hemiplegia or in unilateral ascending spastic paralysis (Mills-Spiller's disease). In these conditions the tapping of the face does not produce a reflexive stretching of the head, but merely a slight vibration. In some instances this mechanical vibration of the head is hard to distinguish from a slight retractive movement. Under favorable conditions this reflex, as every other deep muscle reflex, may possibly be elicited in a normal person. In organic lesions the reflexive head retraction is usually so outspoken that its pathologic significance can hardly be doubted. However, occasional borderline or doubtful reflex conditions are seen.

This reflex has never been found positive in a purely spinal affection. Lesions of the medulla oblongata affecting exclusively the nuclei and sparing the pyramidal tract, such as progressive bulbar palsy, never give a positive head retraction reflex.

This reflex is most pronounced in amyotrophic lateral sclerosis and has also been elicited in lateral sclerosis, cerebrospinal lues, and arteriosclerotic and other diffuse lesions of the brain including essential hypertension. It has likewise been noted in dorsolateral sclerosis and in multiple sclerosis. In advanced cases of amyotrophic lateral sclerosis with bulbar involvement, this reflex is so pronounced that the slightest tapping of the face, even with the finger, produces a brisk jerk of the head backward. The reflex was negative in a patient with amyotrophic lateral sclerosis in whom a flaccid paralysis of the head retractors caused the head to fall forward. Furthermore, it was negative in a patient with the lumbar type of amyotrophic lateral sclerosis in whom the degeneration slowly crept upward and the upper extremities were only slightly affected.

The results of recent research on the pathology of amyotrophic lateral sclerosis explain why the head retraction reflex is strongly positive in this disease. Since the degeneration of the pyramidal tracts can be traced upward from the spinal cord to the cerebral cortex, it is apparent that amyotrophic lateral sclerosis is not only a spinal disease affecting the pyramidal tracts in the lateral columns of the spinal cord, but also an affection of the brain. It really is not an amyotrophic *lateral* sclerosis but an amyotrophic *pyramidal* sclerosis. Furthermore, the frontal and temporal cortices may be affected and may cause the appearance of psychic and organic

cerebral phenomena. The occurrence of the head retraction reflex in all diffuse cerebral lesions is easily explained by their effect on the widespread corticobulbar tracts.

It is remarkable that the head retraction reflex may be positive in dorsolateral sclerosis. In accordance with the findings of recent years, focal signs of degeneration in the white matter and in the ganglion cells of the cortex, similar to those of the spinal cord, may occur in dorsolateral sclerosis. In multiple sclerosis the head retraction reflex is positive only in cases of definite involvement of the brain; it is absent in the purely spinal forms.

The practical importance of this reflex lies in the fact that in some cases it has been the only sign and in others the outstanding objective sign of a supracervical or a suprapontine lesion. Some lesions apparently spinal are not exclusively spinal, but have crept beyond the spinal cord and have affected the corticobulbar tracts. In some cases the positive head retraction reflex is a very helpful diagnostic adjuvant in confirming other findings. In certain remarkable cases, the unexpectedly positive head retraction reflex was the first sign to direct attention to a supracervical lesion, the diagnosis of which was confirmed later by other means. One patient especially impressed me. He was a 60-year-old gardener who complained of weakness of the left leg of several months' duration. At first glance, his gait and his history (he had been working for 16 years as a gardener and had frequently assumed the squatting position) gave the impression that he had an occupational peroneal palsy. But the head retraction reflex was strongly positive and a detailed examination revealed other signs of an amyotrophic lateral sclerosis. It was of the ascending lumbar type, and the head retraction reflex was the only sign to indicate how far upward the involvement of the cerebrospinal axis had extended.

The head retraction reflex may facilitate the differential diagnosis of high cervical cord lesions and systemic degenerations of the spinal cord, such as amyotrophic lateral sclerosis and dorsolateral sclerosis. Various investigators have recently shown how difficult such differential diagnosis may be and how easily even an experienced neurologist may be misled.[2,4] Since systemic degeneration may in the long run affect the supranuclear bulbar tracts and thus produce a positive head retraction reflex, and since this is not to be found in a lesion confined to the high cervical cord, the presence or absence of the head retraction reflex may play a decisive rôle in the differential diagnosis of these affections and eventually may obviate the use of myelography. In one patient in whom a protruded intervertebral disk was suspected and myelography was performed, a strongly positive head retraction reflex indicated clearly that the lesion extended beyond the spinal cord. Further examination proved the case to be one of genuine lateral sclerosis.

This reflex can give invaluable aid in the differential diagnosis

of amyotrophic lateral sclerosis which is sometimes difficult because the Babinski reflex is often absent in this disease. In a patient with a clinical picture of progressive spinal muscular atrophy, a positive head retraction reflex indicates the presence of amyotrophic lateral sclerosis. Furthermore, this reflex is of value in the differential diagnosis of all the conditions accompanied by tetraplegia, such as systemic degenerations (*e. g.*, Charcot-Marie-Tooth disease), cervical myelitis, spinal vascular diseases, tumors, pachymeningitis cervicalis hypertrophica, and polyneuritis. In such differential diagnosis, the behavior of the reflex indicates whether or not the lesion has transgressed the boundaries of the spinal cord. In systemic degeneration of the spinal cord, a positive head retraction reflex indicates extension of the lesion to the brain and so becomes a valuable prognostic sign.

A cerebral lesion involving the leg center, the lobulus paracentralis bilaterally, such as may be due to a parasagittal meningioma, tangential gunshot wound or other traumatic injury of the top of the skull, thrombosis of the superior longitudinal sinus, or Little's disease, may produce a spastic paraplegia of the lower extremities without interfering with the corticobulbar and corticospinal tracts leading to the upper extremities and to the head and face. In such a case, spastic phenomena of the lower extremities would be expected but the head retraction reflex would be negative. I observed only one patient in whom a parasagittal meningioma could be suspected; but the diagnosis was not conclusive. Here may be a further possibility for the utilization of the head retraction reflex.

No patient with meningitis, basilar or other type, has been examined for this reflex that may be present here even in the early stages of the disease. At the beginning of the meningitis, the actual retraction of the head may not be marked; however, muscular resistance and pain may be elicited if an attempt is made to flex the head forward. These conditions favor the appearance of a positive head retraction reflex.

Because of limited experience and lack of pathologic material, no conclusions as to the exact location of the paths of this reflex can be drawn from purely clinical observations. However, it seems certain that a release of cortical inhibition must take place in the muscles that retract the head before this reflex could appear. Therefore the lesion must lie bilaterally on the corticospinal tracts above the anterior motor nuclei of the upper cervical segments. Its exact location is not essential, but it usually lies in the upper rather than in the lower parts of these tracts.

Since the afferent limb of the arc for the head retraction reflex goes through the trigeminal nerve, this reflex must be negative in bilateral trigeminal anesthesia even if a bilateral supranuclear lesion is present. Thus far I have not had an opportunity to examine a patient with such a condition.

Some hypertonia of the head retraction muscles, that is, some kind of latent opisthotonos, is a condition *sine qua non* for the appearance of this reflex. However, a real opisthotonos has never been found in patients with a positive head retraction reflex, and the expected hypertonia of the neck muscles, even in patients with a marked head retraction reflex, has been slight if at all demonstrable.

Marked retraction of the head, together with pronation of the upper and inversion of the lower limbs, is characteristic of the decerebrate rigidity due usually to an interference with the motor centrifugal tracts at the level of the mesencephalon. The head retraction reflex may belong to the syndrome of decerebrate rigidity, since a mild degree of hypertonia of the head retraction muscles is necessary for its appearance and this hypertonia and opisthotonos are among the cardinal signs of decerebrate rigidity. Thus the head retraction reflex would be an expression of the mildest subclinical form of decerebrate rigidity.

I have been unable to find any reference to the reflex phenomenon described herein in the popular English, French and German textbooks on neurology or neurologic diagnosis. Foerster,[1] in the chapter on exaggeration of the reflexes in the domain of the cranial nerves, of his monograph "Motor Areas and Tracts," discussing the behavior of the periosteal reflexes of the face, stated that when the corticobulbar tracts are eliminated "wherever the stimulus may reach the skull or the face, the whole musculature of the face contracts more or less, not only on the stimulated side but also on the contralateral side. Not infrequently the extensors of the head take part in this reflex action in such a way that the head makes a jerk backward."

In his recent work, Wilson[7] notes in the chapter on amyotrophic lateral sclerosis: "In some spastic spinobulbar cases I have found that downward percussion on the chin (mouth shut) provoked contraction of head extensors (deep posterior rotators); so far as is known to me this reflex of upper cervical segments has not hitherto been described." Even Wilson, who had an astounding knowledge of current literature and who cited in this chapter works that appeared in 1932, had overlooked an article on this subject by Nemlicher *et al.*[3] published in 1931. In pseudobulbar palsy, in amyotrophic lateral sclerosis and in bilateral hemiplegia these authors observed a reflex corresponding to the head retraction reflex. They called it mediofacial or faciocervical and considered it a periosteal reflex. They regarded it as pathognomonic for bilateral affections of high location in the pyramidal tracts.

The observation of Weingrow,[6] according to which tapping of the zygomatic or nasal region of the face causes contraction of the facial musculature and a slight movement of the head (the latter due to contraction of the cervical musculature), apparently belongs in the category of this reflex.

The head retraction reflex is so striking that it must also have been observed and described elsewhere. It is noteworthy that this reflex has now been described independently by five authors, three of whom did not refer to the work of the others.

Summary. In bilateral pyramidal lesions situated above the highest cervical cord, tapping of the face brings forth a reflexive retraction by provoking a sudden bending of the head. This head retraction reflex constitutes a reliable sign of bilateral supracervical involvement of the pyramidal tract which may be of importance in the diagnosis of these conditions and in their differentiation from purely spinal affections. Preliminary experiences with this reflex arouse many questions and warrant the suggestion that it be studied further.

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THE URINARY EXCRETION OF BISULFITE BINDING SUBSTANCES BY HUMAN ADULTS ON THIAMIN-LOW DIETS.*

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It is generally accepted today that pyruvic acid is not metabolized properly in the animal body in thiamin deficiency and so may accumulate in abnormal amounts.[14, 20] Clift and Cook[5] utilized the property common to keto acids and aldehydes of combining with bisulfite under certain conditions in a method for the determination of pyruvic acid. In biologic fluids it measures other

* From the thesis presented by Maurice E. Shils to the faculty of the School of Hygiene and Public Health, The Johns Hopkins University, in partial fulfillment of the requirements for the degree of Doctor of Science in Hygiene.

substances in addition to pyruvic acid—the total determined being called the bisulfite binding substances (B.B.S.). Although not specific for pyruvic acid, the method is of value under controlled conditions and has the advantage of being simple and rapid.

Thompson and Johnson[20] were the first to attempt to correlate pyruvic acid and B.B.S. concentrations in the blood of thiamin-deficient animals. Deficient rats and pigeons had a greatly elevated B.B.S. and pyruvic acid content; quantitative estimations showed the rise in B.B.S. to be due entirely to the increase in pyruvic acid. Since then, in keeping with the importance of the subject, a number of papers dealing with human and animal experiments have appeared and are reviewed rather fully by Platt and Lu.[14]

These workers measured pyruvic acid and B.B.S. in the blood and cerebrospinal fluid of beriberi patients. The values for pyruvic acid and B.B.S. in subacute cases were within normal limits or only slightly raised, while in acute cases the increases were quite marked with a decrease occurring quickly following thiamin injection. Taylor, Weiss and Wilkins[19] have found increased blood B.B.S. in untreated human thiamin deficiency as well as in a number of other unrelated conditions. Consequently, an increased B.B.S. value does not necessarily indicate thiamin deficiency. This, in itself, does not eliminate the possibility of using the level of B.B.S. as a measure of thiamin deficiency. Logically, a high level of B.B.S. not caused by thiamin deficiency should remain unchanged on administration of the vitamin, whereas the high B.B.S. caused by the accumulation of pyruvic acid as a result of the vitamin deficiency should quickly decrease. A suitable procedure would seem to include the determination of B.B.S. before and after the ingestion or injection of a standard dose of thiamin.

Evidence was therefore sought concerning the behavior of B.B.S. in experimental human deficiency. Urine, in preference to blood, was analyzed for its B.B.S. content. At the time these studies were made values had not been reported for B.B.S. in urine. Since then Banerji and Harris[2] have reported data on B.B.S. in the urine of men subsisting voluntarily on a thiamin-low diet. Their results differ from those reported here.

Experimental Methods. *Determination of B.B.S. in Human Urine.* The principle of the Clift and Cook procedure[5] is as follows: pyruvic acid forms an addition compound with sodium bisulfite in acid medium. Excess bisulfite is removed with iodine and the bound bisulfite is liberated by the addition of alkali. Standard iodine solution is used to measure the liberated bisulfite.

Preliminary investigation indicated that this procedure cannot be applied directly to urine. The primary obstacle is the presence in urine of reducing substances whose reducing action is greater the higher the pH. These interfering substances often reduce more iodine than the bisulfite liberated in the determination, resulting in very high values and in a poor final end point. Since the interference is very much less at the lower pH where the bisulfite addition compound is formed, efforts were made to determine the

B.B.S. by measuring the excess uncombined bisulfite by titration with standard iodine solution as was done by Ripper in his method for the determination of acetaldehyde.[15] The variable results obtained through volatilization and oxidation by air of the bisulfite caused this procedure to be abandoned.

It was found that 1 mg. of uric acid reduced about 1.5 ml. N/200 iodine solution. Uric acid and some other compounds found normally in urine can account for an appreciable amount of iodine reduction unless means are employed to prevent their interference.

Precipitation by means of phosphotungstic acid and lead acetate proved unsatisfactory because pyruvic acid added to urine which was then subjected to the treatment no longer could be found as B.B.S.

Adsorption of the interfering substances from urine with Lloyd's reagent (Lilly), a hydrated aluminum silicate, followed by permutit, proved more successful. Folin and Svedberg[7] in the determination of sugar used these adsorbents to remove reducing substances. Pyruvic acid is not adsorbed from an aqueous solution and can be recovered quantitatively. Pyruvic acid added to urine which is then put through the adsorption procedure is not destroyed. By this procedure most of the reducing substances are removed, the final end point is much more definite, no frothing occurs, and the urine is clear.

To eliminate the necessity of adsorption with permutit the modification of Hamilton[8] was adopted, whereby acid-treated Lloyd's reagent alone is used. Continuous mechanical mixing of the reagent in the acids shortened the period of preparation. The final washed and dried product was powdered and put through a 40-mesh screen. It was found that this acid-washed adsorbent contained a small quantity of B.B.S. which differed in amount from batch to batch. It was necessary, therefore, to find the blank for each batch. The pH for the dissociation of the pyruvic acid bisulfite compound is about pH 6.0.

The procedure adopted for determining B.B.S. in human urine is as follows: The 24-hour output collected under toluene is diluted to 1500 ml. if below that volume. To 100 ml. of this dilute urine are added 40 ml. 0.125 N oxalic acid and then 32 gm. of the acid-washed Lloyd's reagent. After shaking 4 to 5 minutes the adsorbent is allowed to settle out and the urine is filtered through No. 50 Whatman filter paper (B.B.S. free). Twenty-five ml. aliquots are taken and to each is added 0.6 ml. of approximately 1 M sodium bisulfite solution. After standing 15 minutes at a temperature below 25° C., 1 ml. of 1% starch solution is added. The excess bisulfite is removed with 0.1 N iodine and 1 to 2 drops more iodine are added and allowed to remain for about 3 minutes. The solution is then decolorized with approximately 0.01 N sodium thiosulfate, after which N/200 iodine solution is added to a faint blue. After swirling has stopped, 5.5 ml. of a clear saturated solution of sodium bicarbonate are run in down the sides of the flask to liberate the bisulfite. Two-hundredth N iodine solution is added dropwise from a microburette at a constant rate until a faint blue color persists throughout the solution for a few seconds. This is the final end point.

The differences between the 25 ml. aliquots of a sample done in triplicate usually fell within 0.2 ml. of each other and rarely differed by more than 0.3 ml., as verified by many determinations. Twenty-five ml. aliquots of urine from 4 individuals eating approximately the same kinds of food gave average values between 1.5 and 2.3 ml. N/200 iodine solution.

Since it is quite certain that other substances than pyruvic acid contribute to the B.B.S. of normal and deficient individuals, we prefer to express results in ml. N/200 iodine solution instead of as "pyruvic acid," as has been done by other workers.

Production of Thiamin Deficiency. Two normal young men (A and B) and 2 normal young women (C and D) limited themselves to a diet low in thiamin, but otherwise regarded as adequate as respects essential nutrients. The diets were as follows:

Breakfast: Cereal: unfortified farina or white rice
Pancakes of white flour and egg white with corn syrup (taken by A and C)
White bread or soda crackers with butter

Lunch: Small serving of cheese, American or Swiss
Soda crackers or white bread
Cooked polished rice with cream (occasionally)
Coffee
Milk (one glass by A for first 3 weeks)
Apple (by A and C)

Dinner: Choice of cooked hominy, macaroni, polished rice or spaghetti
Small piece of beef (once weekly by B and D)
White bread and butter
Jello
Coffee or tea

Each subject took a daily supplement of: *a*, salt mixture to supply calcium, iron and magnesium; *b*, acid washed casein, 15 gm.; *c*, autoclaved yeast to supply B complex other than thiamin, 15 gm.; *d*, ascorbic acid, 30 mg.; *e*, vitamins A and D as cod-liver or percomorph oil.

A liberal estimation of the daily thiamin intake calculated from the data taken from two sources[3,23] placed the value at 150 to 180 micrograms for each subject. The daily adult requirements are estimated at 700 to 1000 micrograms.[23] The experimental diets were, therefore, quite low in thiamin. The thiamin : non-fat calory ratio was estimated at no more than 0.12. Diets with a ratio of less than 0.3 are beriberi-producing.[23]

The 2 male subjects restricted themselves to the thiamin-low diet for two periods, once in February and again in June and July of 1939. The first deficiency period lasted 14 days; the deficient diet was continued 3 days more with each individual receiving 5 mg. of crystalline thiamin* daily. In the second period both male subjects and the 2 young women were supplemented with 1 mg. of thiamin for 2 days after beginning the deficient diet. Individual A continued on the deficient diet for 37 days more. On the 38th day 1 mg. of thiamin was injected intravenously for a tolerance test[13]† and the

* The thiamin was a gift of Merck & Co., Inc.

† The measurements of thiamin and the thiamin tolerance test were made by Dr. Victor Najjar of the Harriet Lane Home, Johns Hopkins Hospital. The thiamin was determined by the thiochrome method of Hennessy and Cerecedo.[9]

diet was continued for 2 days more supplemented with 5 mg. of thiamin per day. Individual B consumed the deficient diet without any thiamin supplement for 29 days, received 1 mg. thiamin for the tolerance test on the 30th day and continued on the deficient diet with 5 mg. daily for 5 days more. Individual C ate the deficient diet for 14 days after the 2-day thiamin supplement and then received 5 mg. thiamin for 3 days more. Individual D consumed the deficient diet for 19 days, after which thiamin was given for 2 days.

B.B.S. determinations were made every other day except for the first and last week of each subject's period when they were made every day.

Results. Definite evidence for the low-thiamin intake of the subjects is given by the results (Table 1) of the determinations of thiamin excretion for individuals A and B in the second experiment.

TABLE 1.—EXCRETION OF THIAMIN PER 24 HOURS (IN MICROGRAMS).

	Day on deficient diet.										
	24.	25.	26.	27.	28.	29.	31.	33.	35.	36.	37.
Subject A	7.4	0.0	0.0	0.0	0.0	3.8	3.8	11.9	15.0	0.0	0.0
Subject B	...	3.0	3.0	2.7	3.0						

The range of excretion on a normal diet is usually over 100 micrograms per 24 hours.[13]

Physical examinations of subjects A and B just before the injection of thiamin indicated that both individuals were clinically normal. Electrocardiograms taken before and at the end of the experimental diet were normal.* No symptoms definitely ascribable to the deficiency were noted at any time. The monotony of the dietary schedule caused loss of appetite, and occasional periods of fatigue were experienced by the subjects, but these symptoms could not be ascribed to the lack of the vitamin, since they persisted after thiamin administration.

Further evidence of the low intake of thiamin was afforded by the thiamin tolerance test of Najjar and Holt[13] which was given to subjects A and B at the end of their second experiment. It was repeated after both individuals had been on a normal diet for more than a month. The results are given in Table 2.

TABLE 2.—THIAMIN TOLERANCE TEST GIVEN TO INDIVIDUALS ON THIAMIN DEFICIENT AND NORMAL DIETS.

(Thiamin excretion in micrograms after intravenous injection of 1 mg. thiamin.)

Time after injection (hours).	A—On deficient diet July 10 (38th day).	A—On normal diet August 20	B—On deficient diet July 2 (30th day).	B—On normal diet September 28.
½	58.0	208.0	74.5	211.2
1	0.7	12.4	3.1	17.2
2	1.5	16.8	0.0	8.6
3	Trace	8.1	0.0	6.0
4	0.1	...	0.0	4.6

* The electrocardiograms were made by Dr. Anna Baetjer of the Department of Physiological Hygiene, School of Hygiene and Public Health.

These figures indicate[13] a low intake of thiamin and a need of the body for the vitamin. The degree of retention as shown by the excretion before and after a diet with adequate thiamin is striking.

There was no significant rise in the B.B.S. of any individual during the course of the deficiency, nor was there any change on administration of thiamin. Since the results in the two periods were the same, only data from the second experiment is given in Table 3.

TABLE 3.—B.B.S. IN URINE OF SUBJECTS ON THIAMIN-LOW DIET.
(Per 24 hours in ml. N/200 iodine.)

Day.	Subject A.	Subject B.	Subject C.	Subject D.
1	157	172	134	168
10	128	167	124	182
13	119	157	142	142
15	133	157	136*	134
16	128	144	141*	154
19	115	174	...	142*
20	119	188	...	152*
30	143	146*		
31	133	137*		
38	134*			
39	147*			

* Thiamin administered.

Table 3 indicates a marked fluctuation in the values but all are within the same range. The extreme range of values of A for all the 32 determinations made was 115 to 180 ml. N/200 iodine; of B for 27 determinations 137 to 200 ml. Since the daily fluctuations could be caused only partly by measuring variations (20 ml. maximum) other factors enter, chief among them being probably daily variation in the quantity of food, which did occur. It has been found with rats[18] that the quantity of food intake has a decided influence on B.B.S. values.

Discussion. The results reported here indicate that 29 to 37 days on a thiamin-low diet such as used in these experiments are not long enough for a significant disturbance in intermediary carbohydrate metabolism of normal young adults, if the level of B.B.S. in urine is taken as a criterion.

On the other hand, Banerji and Harris[2] mention briefly that in the urines of 3 individuals on an experimental beriberi-producing diet, the B.B.S. increased three to four times over the initial values in about 1 week. Experience with rats[2,18] indicates that within 2 weeks after being placed on a thiamin-deficient diet, the urinary B.B.S. increases greatly. The report of Banerji and Harris[2] would indicate a similar rapid disturbance in the metabolism of human beings—a finding not substantiated by our observations. The analytic procedure used for human urine is not given in detail by the English workers, but it probably differs from our procedure because the normal B.B.S. (expressed as mg. pyruvic acid) found by them is 140 to 190 mg. per day, whereas the highest value found by us was 63 mg. The difference may be due to the fact that we

removed interfering substances by adsorption. Further proof that the adsorption treatment does not remove pyruvic acid is given by the results with rats where the same procedure was applied.[18]

Perhaps if the deficiency period was extended, increased values for B.B.S. may have occurred.

Comparison with the reports of blood B.B.S. estimations is interesting. Williams, Mason and Smith[22] carried experimental thiamin deficiency to a period of 21 weeks in 4 patients without detecting any elevation in the B.B.S. of blood. Robinson, Melnick and Field[16] found no elevation of blood B.B.S. during a 22-day period of low thiamin intake. Elsom *et al.*[6] reporting a case of experimental human B-complex deficiency found no rise in either blood pyruvic acid or B.B.S. in the fasting state during 9 weeks without thiamin. The work of Platt and Lu[14] indicated little or no increase in blood pyruvic acid or B.B.S. in subacute beriberi.

Inability to find increased B.B.S. values in the blood in individuals on thiamin-low diets where symptoms of the deficiency have appeared[16,22] raises an interesting problem. Several possible explanations present themselves. *A.* The renal threshold for pyruvic acid and B.B.S. may be about the level normally existing. The first evidence of deranged carbohydrate metabolism would then be expected to be found in urine. In this case the B.B.S. or pyruvic acid would rise in the blood only in chronic or severe deficiency when the kidneys were unable to keep the blood level normal. A comparison of the blood and urinary levels of pyruvic acid or B.B.S. at the same time in controlled experiments would help answer this question. Sherman and Elvehjem[17] have found that in thiamin-deficient chicks while the blood B.B.S. level was normal, the B.B.S. value of the excreta (chiefly through the urinary component) was increased threefold. *B.* If the B.B.S. and pyruvic acid renal threshold in humans is not at the normal level for the blood, then deficiency symptoms may appear with very little, if any, increases in the blood and urinary concentration of these substances.

High values for B.B.S. in blood have been reported in pellagrins[11,12] which decreased upon injection of cocarboxylase with remission of neurologic symptoms; in pregnancy,[2,4] in beriberi[14] and in inebriation,[24] all being conditions associated with chronic malnutrition. However, there are also reports of cases of chronic thiamin deficiency where there was no rise in blood B.B.S.[14,16] The blood B.B.S. level would thus seem to be an unreliable index of thiamin nutrition. Increased blood pyruvic acid concentration has been found in the above conditions[4,14,24] as well as subnormal thiamin excretion.[13,16]

There are reports in the literature of increased blood pyruvic acid concentration[6,14] with no concomitant increase in B.B.S. This is difficult to understand because it is well established[5,14,17,20] that pyruvic acid binds bisulfite under the conditions of the Clift and Cook procedure.[5]

The literature concerned with the appearance of symptoms in experimental human deficiency is also not in agreement. No symptoms attributable to thiamin deficiency were found in the experiments described here. Likewise, Wang and Yudkin[21] report no objective symptoms in 3 volunteers on a diet low in thiamin (100 to 150 micrograms daily) after 10 to 14 days.

Alvarez *et al.*[1] noted no symptoms in 3 individuals on a low-thiamin diet for 6 weeks. Williams and coworkers[22] found symptoms, but as they state, "the onset of these symptoms was much later than had been anticipated." (Evidently from the report of Jolliffe *et al.*[10]).

Other workers have found symptoms occurring rather soon after restriction to the deficient diet. Jolliffe and coworkers[10] found symptoms in 4 out of 5 subjects, with the first showing objective signs as early as the 5th day. The addition of thiamin to the thiamin-low diet caused all symptoms to disappear within 3 days. The deficient diet contained more thiamin than any other discussed here (474 micrograms daily). Indeed, Wang and Yudkin[21] have recalculated the thiamin content of the diet used by Jolliffe *et al.*[10] according to the tables of Fixsen and Roscoe[3] and have found it to contain 750 to 1000 micrograms, which is within the range of normal requirement.

Robinson, Melnick and Field[16] observed aching of the calf muscles after exercise as early as the 12th day on a deficient diet, which increased as the diet continued. Paresthesias of the lower extremities and dyspnea on mild exertion also occurred before 22 days. There were no changes in the electrocardiogram. Elsom *et al.*[6] found clinical manifestations and metabolic changes evident only after 5 weeks on the experimental diet which was deficient in the whole B complex.

These divergent results may possibly be explained by the facts that: *a*, individuals differ in their requirements for the vitamin; *b*, the tables of the thiamin content of foods are admittedly far from exact and thus accurate calculation is impossible; or, *c*, conditions of experiments in the several laboratories varied considerably.

On one point all papers,[13,16,21,22] including this one, dealing with thiamin excretion agree. All relate a decrease during the deficiency period. It is interesting to note that Banerji and Harris[2] report increased urinary B.B.S. values in human beings while thiamin was still being excreted at a moderately high level. This finding is at variance with the results reported here where normal urinary B.B.S. values were still found with very low thiamin excretion.

The work reported here together with the recent literature on the subject seems to indicate that in adult humans, at least, the level of thiamin excretion, especially after a test dose, is a more sensitive and reliable indicator of the level of thiamin nutrition than are measurements of B.B.S. and pyruvic acid. However, the concentration of thiamin in blood and urine gives no information on the

condition of intermediate carbohydrate metabolism in the body. More research is necessary on the relationships between B.B.S., pyruvic acid and thiamin levels in blood and urine.

Summary. 1. The method for determining bisulfite-binding substances (B.B.S.) is modified and adapted to urine. Interfering substances in urine are removed by adsorption on a preparation of Lloyd's reagent. The pH for the dissociation of the pyruvic acid-bisulfite addition compound has been found to be about pH 6.0.

2. Four normal young adults, 2 men and 2 women, restricted themselves to a diet low in thiamin for varying lengths of time, the maximum being 37 days. No rise in B.B.S. excretion was found during the course of the experiments. Likewise no symptoms were noted, although thiamin excretion was reduced to a very low level.

3. In connection with the results reported here, the recent literature on experimental human thiamin deficiency is briefly reviewed.

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THE RELATIONSHIP BETWEEN THE SPECIFIC GRAVITY AND THE PROTEIN CONTENT IN HUMAN SEROUS EFFUSIONS.

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The purpose of this investigation was to determine whether a relationship exists between the specific gravity and the protein content of human pathological serous effusions. Although a definite relationship between these two has been established in human

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blood[4] and in the blood, lymph and edema fluids of dogs,[10] there is considerable disagreement in the literature as to whether there is such a correlation in the transudates and exudates obtained from human serous cavities.[1,7,8] Reuss, in 1881, evolved a formula expressing this relationship in serous fluids which is partially correct.[9]

Methods. All determinations on fluids were done within 48 hours, since it was found by experiment that even when kept in the icebox the intact protein diminished significantly after that time, although the specific gravity remained about the same. The fluids were centrifuged initially for 10 minutes to remove clots and cells. They were re-centrifuged if further clotting occurred, a not uncommon happening particularly in exudates even after 24 hours. The effect of clotting on the specific gravity and the protein content was found to be insignificant in both exudates and transudates. None of the fluids was markedly hemorrhagic.

The specific gravity was determined by pyknometer and, with 10 exceptions, in duplicate. Ten cubic centimeter pyknometers were fitted with rubber caps to slow the rate of evaporation. This was found to be as efficacious in this regard as the application of vaseline to the capillary stopper as advocated by Moore and Van Slyke.[4] On each occasion the fluid and distilled water were weighed in the pyknometers at room temperature which during these experiments varied from 21.5° to 29.5°. The weight of the fluid was divided by the weight of the water from the same pyknometer, thus giving the specific gravity at room temperature, $D\frac{t^\circ}{t^\circ}$. The specific gravity thus obtained was then corrected for temperature by means of the following formulæ:

(1) $$D\frac{20^\circ}{4^\circ} = D\frac{t^\circ}{t^\circ} \times d_w t^\circ + (t^\circ - 20^\circ)\ 0.00026$$

(2) $$D\frac{20^\circ}{20^\circ} = D\frac{20^\circ}{4^\circ} \div d_w 20^\circ$$

(All temperatures are recorded in degrees Centigrade.)

The figures for the density of water at the various room temperatures ($d_w t^\circ$) corrected for expansion and air buoyancy were obtained from Peters and Van Slyke.[6] The coefficient of expansion of the fluids was found to average 0.00026 by experiment in one transudate and one exudate for the range of temperature at which the experiments were conducted.* Within this range of temperature, the change of $D\frac{t^\circ}{t^\circ}$ (the specific gravity at room temperature) to $D\frac{20^\circ}{20^\circ}$ (the specific gravity with both fluid and water at 20° C.) added, at most, 0.00029 to the specific gravity. For practical purposes, therefore, no correction need be made for the specific gravity of the fluid as determined at room temperature although such a correction was made in these experiments.

The protein content was determined by the micro-Kjeldahl method, the final nitrogen reading, after Nesslerization, being done by the photoelectric cell colorimeter. The determination of the non-protein nitrogen multiplied by 6.25 was subtracted from the total nitrogen multiplied by 6.25 to give

* Done through the kindness of Dr. S. Howard Armstrong, Jr., Department of Physical Chemistry, Harvard Medical School.

the total protein content. In a few instances the non-protein nitrogen was elevated as high as 155 mg. per 100 cc. This had no significant effect on the results.

Results. The specific gravities and protein contents of 53 fluids were determined consisting of 3 pericardial, 12 peritoneal and 38 pleural fluids.

In Figure 1 are recorded these determinations with the specific gravity expressed as $D\frac{20°}{4°}$, the more usual definition of specific gravity. In Figure 2 are the same determinations but with the specific gravity expressed as $D\frac{20°}{20°}$. This is the definition used by

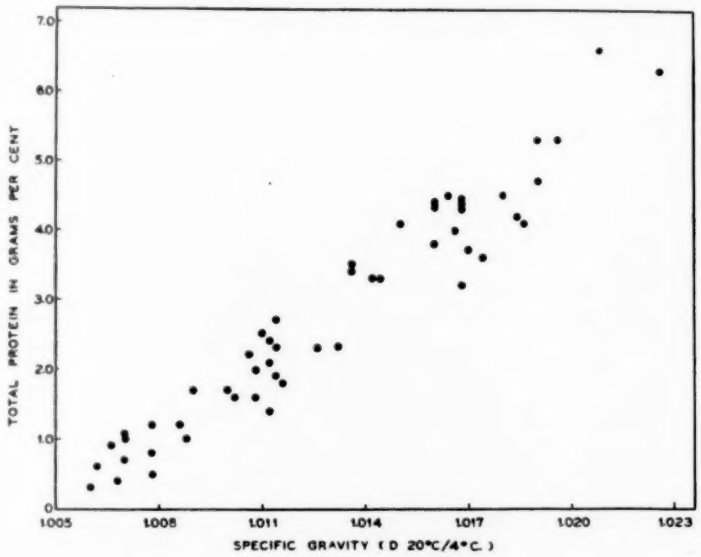

FIG. 1.—The specific gravity, expressed as $D\frac{20°}{4°}$, and the protein content, expressed in grams per 100 cc., of 52 human serous effusions.

Moore and Van Slyke[4] and Weech *et al.*[10] in their work on blood, lymph and edema fluid. As shown by comparison of the two charts, this change in definition results in an increase roughly of 0.003 in the specific gravity. In the literature there is usually no agreement on or no recognition of such a change. In the Kagan "falling drop" proteinometer, the specific gravity is expressed as $D\frac{25°}{25°}$, while in the usual laboratory hydrometer ("urinometer"), it is recorded as $D\frac{15.5°}{15.5°}$.

As shown in Figure 2, there is a good linear correlation between the specific gravity and the protein content of both exudates and transudates. This is expressed by the formula:

$$P = 353\ (G - 1.0076)$$

where P = the protein content in grams per 100 cc.

and G = the specific gravity expressed as $D\frac{20°}{20°}$.

This is the same formula derived by Weech *et al.*[10] for transudates from the blood. By this formula the maximum error in the determination of the protein content of effusions from their specific gravity is the same as that of the blood, *i. e.*, 0.6 gm. per 100 cc.[4]

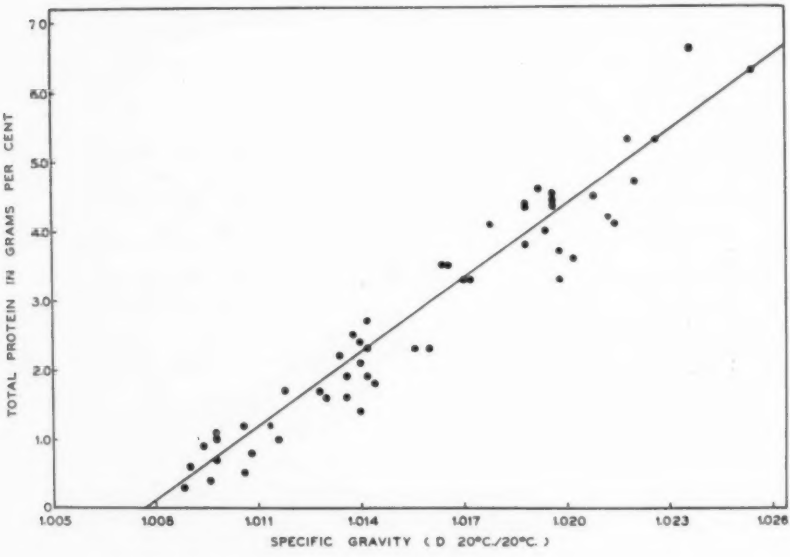

FIG. 2.—The specific gravity, expressed as $D\frac{20°}{20°}$, and the protein content, expressed in grams per 100 cc., of 52 human serous effusions.

In Figure 3 are shown the same determinations as in Figure 2 but with appropriate symbols for the diseases of the patients from whom the fluids were obtained. Although the general rule holds true for the separation of transudates from exudates on the basis of specific gravity (or protein content), there are many exceptions.[5] There appear to be at least three factors which *may* be responsible for this. The first is the resorption of the fluid with resultant concentration of the unabsorbed protein. This is best illustrated by the occasional cardiac fluid of high specific gravity and protein content in Figure 3. The protein content and specific gravity of cardiac fluids has been shown to increase following diuresis.[2,3]

Secondly, protein long in a serous cavity may break down with loss of nitrogen into the blood. This theory is advanced as an explanation for a fluid which was the one exception to the specific gravity, protein relationship in our cases. This fluid, which was not charted, was obtained from the pleural cavity of a patient suffering from migratory phlebitis and showed the exceptionally high specific gravity of 1.0522, a protein content of but 5.2 gm. per 100 cc. and a non-protein nitrogen of 39 mg. per 100 cc., all done in duplicate. The cholesterol was 148 mg. per 100 cc. in the fluid. A third factor which may influence, by lowering, the specific gravity (and protein content) of an effusion is a low serum albumin. The cases illustrat-

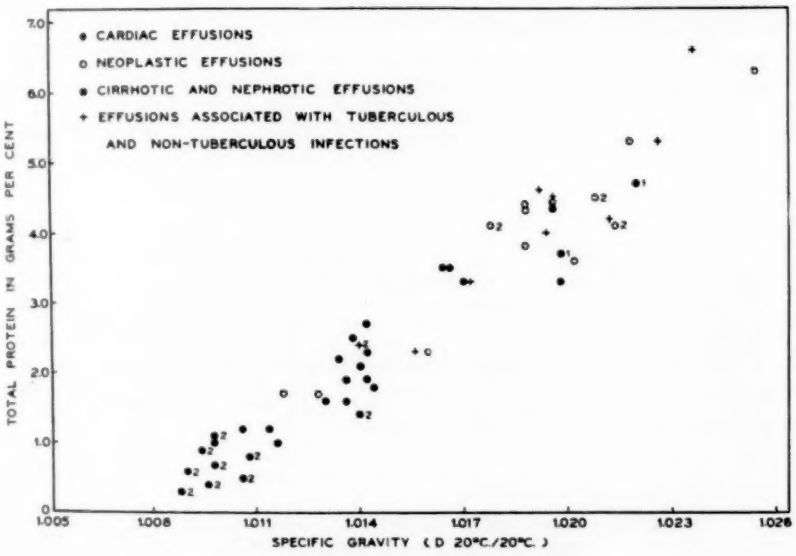

FIG. 3.—The specific gravity, expressed as $D\frac{20°}{20°}$, and the protein content, expressed in grams per 100 cc., with symbols for the associated disease in 52 human serous effusions. 1. Heart disease associated with scleroderma. 2. Serum albumin below 3 gm. per 100 cc.

ing this are noted in Figure 3. This does not appear to play a constant rôle since cases of hypoalbuminemia may have a high protein content in their effusions and *vice versa*.

In a few instances the Kagan "falling drop" proteinometer was used for the determination of the specific gravity of blood serum and of serous fluids of high protein content. In the case of serum, the result thus obtained was less than 0.001 above that obtained by pyknometer, an insignificant difference. In the serous effusions, on the other hand, the specific gravity by the "falling drop" method was as much as 0.0026 above that determined by pyknometer. This presumably is due to differences in physical characteristics.

Summary. Accurate determinations of the specific gravity and protein content was done in 53 serous effusions obtained from the pericardial, peritoneal and pleural cavities of human beings. With one exception there was found to be a linear relationship between the protein content and the specific gravity which was as close as that in the blood. The formula expressing this relationship is the same as that found by Weech *et al.* in the lymph and edema fluid of dogs.[10]

The specific gravity and protein content of the various effusions are considered in relation to the diseases of the patients from whom they were obtained. The factors which may influence the specific gravity and protein content are discussed.

The Kagan "falling drop" proteinometer was found to be less accurate for the determination of the specific gravity of serous effusions than of blood serum.

I wish to express my thanks to Dr. Otto Schales, of the Chemical Laboratory of the Peter Bent Brigham Hospital for his help and advice and to the Misses V. Burke and E. Heller for their technical assistance.

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IMMUNE RESPONSE IN DRUG TREATED CASES OF PNEUMOCOCCAL PNEUMONIA.*

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The host response to the antigenic action of invading pneumococci has long been a subject of study. As early as 1891 the Klemperers[4] demonstrated that serum taken from pneumonia patients after the crisis displayed curative properties for experimentally infected

* This work was made possible by a grant from the Eli Lilly Company, Indianapolis, Ind.

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rabbits. Further work, by authors too numerous to mention, has revealed the character of the various antibody components and their relation to the course of the disease. It is now known that in patients with pneumonia in whom the disease has not been altered by specific therapy, these protective antibodies may first make their appearance as early as the 3d or 4th day of the disease even though crisis and recovery may not take place for several days. This initial appearance of antibodies is usually in a low titre and they have been found to reach their height about the time of crisis. Following defervescence, the antibody titre may remain high for some time but usually begins to show a decrease in 10 to 14 days.

The theory upon which the serum therapy of pneumonia is based has had its inception and elaboration in these investigations into the immune response to the pneumococcus. Though the clinical features of the disease have been greatly altered by serum therapy, such treatment did not necessitate any change in our understanding of the biology of the pneumococcus or the response of the host. This treatment consists simply of the transfer of artificially induced immune substances from an animal to the human. Little of the recent work concerned with serum therapy has been done in an attempt to correlate it with our previous knowledge, but has been directed largely toward technical improvement in the production and administration of serum.

With the advent of sulfapyridine therapy in pneumococcal infections an entirely different problem is being faced. The exact mode of action of the drug has not been shown, nor do we know much of its effect upon the immune response of the host. There is, of course, the possibility that the drug may actually interfere with the immunologic response of the host to the infection. Edwards, Kircher and Thompson,[2] however, in a study of 26 cases of pneumococcal pneumonia treated with sulfapyridine, observed no alteration in type-specific and species-specific agglutinin response or the dermal reactivity to the type specific polysaccharide. They also observed no constant relation of the heterophile antibody titre to the clinical course of the pneumonia or to the other antibody responses following sulfapyridine therapy.

This report embraces observations on the presence of agglutinins, mouse-protective power and the polysaccharide skin test in 77 patients treated with type-specific serum and sulfapyridine; 36 patients treated with sulfapyridine and pneumococcus antigen; 14 patients treated with sulfapyridine alone and 2 patients who entered the hospital after the crisis and consequently received no specific therapy. These 129 patients were distributed over Types I, II, III, IV, V, VII, and VIII; 112 of them recovered, 17 died. Observations are also presented on 4 cases of Type XIV pneumonia on which only agglutinin studies and polysaccharide skin tests were done, as the Type XIV pneumococcus is usually avirulent for mice.

Method of Study. Polysaccharide* skin tests were done on each patient before therapy was instituted, about 3 hours after serum therapy, in 24 hours, and at 2- to 5-day intervals thereafter during the hospital stay. Most of the patients were hospitalized for about 2 weeks; a few left earlier, while some were observed over a period of several weeks. Thus, there was considerable variation in the length of time the patients were observed, but all were seen for at least a week after the temperature became normal. Skin testing with the type-specific polysaccharide was done as described by Francis,[3] Edwards, Hoagland and Thompson[1] and others, using 0.05 cc. of a dilution of 1:10,000, intracutaneously, with normal saline control. All tests were performed by the same person (L. L. T.), thus eliminating any variation due to individual differences in performance or interpretation. In a small series of patients an attempt was made to demonstrate the passive transfer of skin sensitivity (J. C. E.).

Blood specimens for the determination of agglutinins and mouse protective tests were secured before therapy, the day following therapy and at 2- to 5-day intervals thereafter, a special effort being made to secure one specimen at the time of crisis and one specimen just before death in those patients who died. Blood specimens were submitted to the Eli Lilly Research Laboratories, where agglutinin determinations and mouse protective titres were run. No data were available to those performing these tests except the type of pneumococcus with which the patient was infected. The work was done under the direction of Dr. H. M. Powell.

Agglutinations were done in the usual manner with serum dilutions of 1–5, 1–10 and 1–20. The mouse-protective titre figures represent the number of minimum lethal doses of pneumococci against which 1 cc. of a given serum protected. In arriving at this figure each serum sample was tested at 7 different levels (0-10,000,000). The simple titration figures are used in recording the results and no attempt has been made to reduce them to the standard therapeutic unit.

Pneumococcus vaccine† was given to a group of 10 normal individuals to note any alteration in the polysaccharide skin test and the mouse-protective titre caused by the administration of such antigen.

Method of Treatment. The cases were divided into three series depending upon the therapy received. One series of patients was treated with type-specific rabbit serum and sulfapyridine. This series was subdivided into two groups, depending upon the amount of serum used; (*A*) On the basis of the suggestion that fractional doses of serum and sulfapyridine if used in combination would be as effective as maximum doses of either agent used alone,[6a] a selected group of 37 patients, entering the hospital within 96 hours of onset and having but one lobe involved, was given minimum doses (40,000–60,000 units) of type-specific serum and only 0.5 gm. of sulfapyridine at 4-hour intervals. Our clinical results are being published elsewhere.[8] Suffice it to say here that a large percentage

* Dr. Lewellen Sale, Jr., helped in preparation of the polysaccharide.

† Supplied by Eli Lilly & Co. Each cc. of polyvalent antigen contained:

4	billion	pneumococci	Type I
4	"	"	" II
1	"	"	" III
2	"	"	" IV
2	"	"	" V
1	"	"	" VII
1	"	"	" VIII
1	"	"	" XIV
4	"	"	DRI

of such patients responded favorably to this therapy. (*B*) This group comprises all other patients who received the combination of type-specific serum and sulfapyridine. These were patients who, for a variety of reasons, were regarded as sufficiently ill to demand full doses of serum and full doses of drug.

The second series of patients was given sulfapyridine and pneumococcus antigen. The use of pneumococcus antigen was stimulated by recent experimental studies[5,6b] suggesting that sulfapyridine would be more efficient in a patient also receiving pneumococcus antigen. Each patient received 1 cc. of polyvalent antigen (pneumococcus vaccine as mentioned above) every 6 to 12 hours. A total of 8 cc. was given during the first 4 days of hospitalization. Sulfapyridine was given in maximum dosage of 1 gm. per hour for 4 doses, followed by 1 gm. every 4 hours until the temperature had remained normal for 2 days, when the dose was cut in half.

The third series of patients was given sulfapyridine alone. Here also the maximum dosage scheme was utilized.

In all patients receiving the larger dosage of sulfapyridine, the oral administration was supplemented by the sodium salt given intravenously when necessary. Indications for such supplementary therapy were inability of the patient to retain the drug by mouth, or lack of response to therapy in the face of insufficient blood concentrations. Five to 10 mg. per 100 cc. were considered adequate levels with an optimum of 7.5 to 8 mg. per 100 cc. However, there was good clinical response in many cases with levels below 5 mg. per 100 cc. so no attempt was made to attain a higher level. Thus, there was some variation in the total amount of sulfapyridine received by the individual patients. The drug was discontinued after 4 days of normal temperature.

Results and Discussion. *Polysaccharide Skin Test.* It is expected on the basis of previous studies that a large percentage (95%) of patients recovering spontaneously from a pneumococcal pneumonia should give a positive dermal reaction with type-specific capsular carbohydrate.[1] The titre of type-specific antibody must be considerable before the skin test is positive, and where no antibodies have been added (*i. e.*, no serum given) the skin tests may remain negative even where there are sufficient antibodies present for recovery. It is also recognized that the test may become positive in cases which may later prove fatal due to extrapulmonary foci of infection such as meningitis, empyema and endocarditis.

Analysis of the series of patients receiving combined serum-sulfapyridine therapy reveals that in Group *A* (Table 1), where the smaller doses of serum were used, 16 of 37 (45%) of the patients showed a positive reaction. In Group *B*, where the maximum doses of serum were used, 18 of 32 cases (56%) showed a positive test at some time during the period of observation. Thus, of a total of 69 patients, 34 (49%) showed a positive dermal reaction (Table 2).

TABLE 1.—SUMMARY OF ALL RECOVERED CASES.

Therapy.*	No. of cases.	Pos. S88 skin tests.	Agglutinins. 1–5.	Agglutinins. 1–10.	Agglutinins. 1–20.	Mouse protective titres. Less than 1000.	Mouse protective titres. 1000 to 1,000,000.	Mouse protective titres. 1,000,000 or more.
Type I:								
100,000 units or more serum	15	5	3	1	4	0	0	13
Less than 100,000 units serum	14	6	0	1	0	0	1	13
Antigen	2	1	0	0	1	0	0	2
Sulfapyridine alone	5	1	0	0	0	0	3	2
Type II:								
None	1	1	0	0	1	0	0	1
100,000 units or more serum	5	2	0	0	5	0	0	5
Less than 100,000 units serum	5	4	0	1	4	0	0	5
Antigen	1	0	0	0	1	1	0	0
Sulfapyridine alone	3	0	0	0	1	0	2	1
Type III:								
100,000 units serum	2	2	0	1	1	0	2	0
Antigen	20	4	2	3	1	11	4	5
Sulfapyridine alone	1	0	0	0	0	0	1	0
Type IV:								
None	1	1	0	0	0	0	1	0
Antigen	5	3	0	1	1	0	1	4
Sulfapyridine alone	1	0	1	0	0	0	1	0
Type V:								
100,000 units serum or more	2	1	0	0	1	0	0	2
Less than 100,000 units serum	3	0	0	0	3	0	0	3
Antigen	1	0	0	0	0	0	1	0
Sulfapyridine alone	2	0	1	0	0	0	2	0
Type VII:								
100,000 units serum or more	6	5	0	1	5	0	0	6
Less than 100,000 units serum	1	0	0	0	1	0	0	1
Antigen	2	2	0	0	2	0	1	1
Sulfapyridine alone	1	1	0	0	0	0	0	1
Type VIII:								
100,000 units or more serum	2	1	0	0	2	0	0	2
Less than 100,000 units serum	12	5	0	5	5	0	6	6
Antigen	1	0	0	0	1	0	0	1
Type XIV:								
100,000 units or more serum	2	2	0	0	2			
Less than 100,000 units serum	2	1	1	0	1			

TABLE 2.—SUMMARY OF RECOVERED CASES TREATED WITH SULFAPYRIDINE AND SERUM.

Type.	No. of cases.	Pos. 888 skin tests.	Agglutinins. 1–5.	Agglutinins. 1–10.	Agglutinins. 1–20+.	Mouse protective titre. Less than 1000.	Mouse protective titre. 1000 to 1,000,000.	Mouse protective titre. 1,000,000 or more.
I	27	11	3	2	4	0	1	26
II	10	6	0	1	9	0	0	10
III	2	2	0	1	1	0	2	0
V	5	1	0	0	4	0	0	5
VII	7	5	0	1	6	0	0	7
VIII	14	6	0	5	7	0	6	8
XIV	4	3	1	0	3			
Total	69	34	4	10	34	0	9	56

* All cases also received sulfapyridine.

Tables 1 and 3 also show the results of the skin tests of those patients treated with sulfapyridine and antigen. Ten of 32 patients (31%) showed a positive polysaccharide test. Of the series of patients receiving sulfapyridine alone (Tables 1 and 4), of 12 patients, 2 (15%) showed positive reactions. In further study of

TABLE 3.—SUMMARY OF RECOVERED CASES TREATED WITH SULFAPYRIDINE AND ANTIGEN.

Type.	No. of cases.	Pos. S8S skin tests.	Agglutinins. 1–5.	1–10.	1–20+.	Mouse protective titre. Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
I	2	1	0	0	1	0	0	2
II	1	0	0	0	1	1	0	0
III	20	4	2	3	1	11	4	5
IV	5	3	0	1	1	0	1	4
V	1	0	0	0	0	0	1	0
VII	2	2	0	0	2	0	1	1
VIII	1	0	0	0	1	0	0	1
Total	32	10	2	4	7	12	7	13

TABLE 4.—SUMMARY OF RECOVERED CASES TREATED WITH SULFAPYRIDINE ALONE.

Type.	No. of cases.	Pos. S8S skin tests.	Agglutinins. 1–5.	1–10.	1–20+.	Mouse protective titre. Less than 1000.	1000 to 1,000,000	1,000,000 or more
I	5	1	0	0	0	0	3	2
II	3	0	0	0	1	0	2	1
III	1	0	0	0	0	0	1	0
IV	1	0	1	0	0	0	1	0
V	2	0	1	0	0	0	2	0
VII	1	1	0	0	0	0	0	1
Total	13	2	2	0	1	0	9	4

TABLE 5.—SUMMARY OF ALL DEATHS.

	No. of cases.	Pos. S8S skin tests.	Agglutinins. 1–5.	1–10.	1–20+.	Mouse protective titres. Less than 1000.	1000 to 1,000,000.	1,000,000 or more.
Sulfapyridine and serum:								
Type I	3	0	0	0	0	2	1	0
II	3	0	0	0	3	0	0	3
V	3	1	0	0	2	1	0	2
VII	1	1	0	0	1	0	1	0
VIII	2	0	0	0	2	0	0	2
Sulfapyridine and antigen:								
Type III	4	0	1	0	0	2	2	0
Sulfapyridine alone:								
Type IV	1	0	0	1	0	0	1	0
Total	17	2	1	1	8	5	5	7

Tables 2 and 3 the striking failure of Type III cases to develop positive skin tests is noted. If these Type III cases are excluded from these two series, there remain 12 cases treated with sulfapyridine and antigen, giving 6 (50%) positive reactions and 12 cases treated with sulfapyridine alone giving 2 (16%) positive reactions.

The low percentage of positive dermal reactions in these cases recovering from pneumonia is surprising. In cases where the skin test remains negative in spite of good response to adequate amounts of serum, it may be well to use higher dilutions of the type-specific polysaccharide than 1–10,000.

There were positive polysaccharide tests in 2 patients who subsequently died. None of the other 15 who died ever showed a positive reaction. One of the positive reactions occurred in a Type V case where the reaction became positive immediately after the administration of serum. The test subsequently became negative and remained so despite a high agglutinin titre and mouse protective titre. Death occurred 9 weeks after admission and autopsy revealed a vegetative endocarditis and meningitis. The other positive test occurred in a patient with a pneumonia of Type VII. The test became positive after administration of 200,000 units of serum, at which time the temperature dropped to normal. The patient seemed to be recovering nicely but on the 10th day developed serum sickness and one day later a thyroid crisis occurred in spite of the previous administration of iodine in large quantities. The patient died with a terminal temperature of 41.5°. The polysaccharide skin test was positive only 2 hours before death.

Two patients showed positive skin tests on admission to the hospital. One (Type IV) had had a crisis and was clinically well, therefore, raising no question as to therapy. The other case, a Type II infection, was admitted the 8th day of the disease and was still critically ill with a temperature of 39.5° C. On the basis of the positive reaction specific therapy was withheld, and in 12 hours clinical crisis occurred and an uneventful recovery ensued. It is probable that in the latter case, had the skin test not been done, large doses of both serum and sulfapyridine would have been given unnecessarily.

Thus it seems that the presence of a positive polysaccharide skin test may be expected in about one-half of the patients receiving less than optimum amounts of serum combined with sulfapyridine. A higher percentage of positive reactions is seen in individuals receiving more nearly maximum amounts of serum with sulfapyridine. An even smaller percentage of positive reactions is seen in cases treated with sulfapyridine and antigen. The antigen, in the small number of patients studied, appeared to increase the number of positive reactions over those occurring when sulfapyridine alone was given. A negative skin test in a patient treated with sulfapyridine does not forecast death; but, on the other hand, a positive reaction is far more significant and is of value prognostically and as a guide for limitation of further therapy.

The blood serum of 5 patients, who gave positive type-specific polysaccharide skin tests after serum therapy, was injected intra-

cutaneously (0.2 cc.) in 24 healthy persons with negatively reactive skins. Twenty-four hours later 0.03 cc. of 1:10,000 solution of type-specific polysaccharide was injected in the same area. Negative results were obtained. Several positive results were obtained when the polysaccharide was injected within 2 or 3 hours after the injection of serum. This suggests the absence of a reagin or a true Prausnitz-Küstner reaction.[7]

Agglutinins. The various tables show the results of our study of agglutinin titres in the patients observed. In none of the cases were agglutinins present on admission. The titre was frequently at its height in the first specimen drawn after the administration of serum. However, in some instances the titre continued to rise for several days thereafter. An analysis of the tables shows that of the 69 cases receiving sulfapyridine and serum, 48 (69%) showed agglutinins of some titre at some time during the period of observation. The lowest agglutinin response was seen in Type I infections where only 9 of 27 (33%) showed an appreciable titre. All of the other types given serum showed the appearance of agglutinins in a high percentage of cases.

Of the 32 cases receiving sulfapyridine and antigen therapy, 13 (40%) showed agglutinins in a titre of 1–5 or more. If, however, the Type III cases are excluded there remain 12 cases, 7 of whom (58%) showed agglutinins. Of the 20 cases of Type III infection only 6 (30%) showed agglutinins and only 1 of these reached a titre of 1–20.

Of the 13 cases of pneumococcic pneumonia treated with sulfapyridine alone, only 3 (21%) showed an appreciable titre. There was only 1 Type III case in this group and it showed no response.

Of the 2 patients who recovered without therapy, 1 (Type II) showed a satisfactory response, while the other (Type IV) showed no agglutinins at dilutions of 1–5 or above, despite a positive skin test and satisfactory mouse-protective power.

The agglutinin response was also studied in 17 patients who died. Nine of these cases showed agglutinins in a titre of 1–5 or more, 7 of them rising to 1–20 or above. All 7 cases with the high titre, however, were confined to the group receiving 100,000 or more units of serum. It is interesting to note that in 6 of these cases upon whom blood specimens were collected within a few hours of death, only 1 showed a decrease or disappearance of the agglutinins. The other 5 maintained a titre of 1–20 or above until death. There was 1 death in the group treated with sulfapyridine alone. This case was due to Type IV pneumococcus and during the period of observation showed an increasing mouse-protective titre (0–10,000), and agglutinins appeared in 1–10 dilution, but the polysaccharide skin test remained negative. There were 4 deaths in Type III infections, all of whom received sulfapyridine and antigen. Two of these

cases never manifested any antibody response, either polysaccharide skin test, agglutinins or mouse-protective power. The other 2 showed an appreciable mouse-protective titre (10,000 or above), but only 1 showed agglutinins in 1–5 dilution.

In conclusion, one might say from our experience that agglutinins appear more promptly and in highest percentage in those cases treated with serum and sulfapyridine. The series of patients treated with sulfapyridine and antigen developed agglutinins to a less degree than those treated with sulfapyridine and serum, but definitely to a greater degree than those treated with sulfapyridine alone. It seems that the presence of agglutinins in a titre of 1–5 or higher, or even in increasing titre, is no assurance of recovery and that a positive polysaccharide skin test is a more accurate prognostic sign.

Mouse-Protective Power. The combined phenomena of agglutination, precipitation, and opsonization are complement forces which contribute to the total protective power of the animal against invading pneumococci. That there is a close correlation between the protective power and the various antibodies has been well shown. Sulfapyridine, however, is an additional factor which must be considered in evaluating the protective power of the sera from the patients in this series. All of the patients received sulfapyridine and even the small amounts present in the serum may have enhanced its protective power for mice. That this factor played a large part, however, seems unlikely as many of the samples taken while the blood sulfapyridine levels were at their height, failed to show any protective properties. It is recognized that the agglutinin observations and the mouse-protective power as run are not comparable quantitatively. The mouse-protective test is a more delicate index of antibody response. Thus, there may be evidence of mouse protection without demonstrable agglutinins. On the other hand, in the presence of agglutinins a rather high mouse-protective power is expected.

Though the sera were tested at seven different levels, for purposes of analysis and discussion the titres have been divided into three classes. The lowest class includes all of those below 1000 M.L.D., the second includes those of 1000 to less than 1,000,000, while into the third are those of 1,000,000 or more.

Of the cases treated with sulfapyridine and serum almost every one that recovered showed a high mouse-protection titre. In fact, of the 30 patients receiving 100,000 or more units of serum, only 2 failed to show a titre of 1,000,000 or more; both of these cases were Type III infections. Only 7 of 35 cases receiving less than 100,000 units of serum failed to show a titre of 1,000,000 or more, and 6 of the 7 were Type VIII cases. In none of the recovered patients receiving serum did the titre remain below 1000, and in 86% of the cases it was 1,000,000 or more at some stage of the disease.

Comparable mouse-protective power cannot be shown for the two series receiving sulfapyridine and antigen or sulfapyridine alone. Only 13 of the 32 cases (40%) who recovered with sulfapyridine and antigen showed a titre of 1,000,000 or more, while 12 (37%) had titres of less than 1000. It seems significant, however, to state that of these showing comparatively little response, 11 were Type III infections. Stated differently, 11 of 20 cases (55%) of Type III pneumonia who recovered under sulfapyridine-antigen therapy failed to show any appreciable mouse-protective power in the serum. If the Type III cases are excluded from this series, 9 of 12 (75%) showed titres of 1,000,000 or more, and only 1 of the 12 (8.3%) failed to show any appreciable protective power. These figures then compare favorably with those seen above in the serum-sulfapyridine treated group.

Thirteen patients who received sulfapyridine alone recovered. Analysis of the results of mouse-protection tests in these cases shows that 4 (30%) developed a titre of 1,000,000 or more, while the remaining 9 cases showed a titre of above 1000. Inasmuch as there was only one Type III pneumonia in this group, little change would be wrought in these figures by excluding this case.

The mouse-protective titre in the 2 cases recovering without therapy reveals that the titre in one Type IV case was only 10,000. This was the case that did not show agglutinins. One Type II patient had a titre of 10,000,000 on admission.

Analysis of the mouse-protective power in the 17 deaths reveals that most of the patients treated with serum and sulfapyridine (7 of 12) showed a titre of 1,000,000 or more, but that 3 showed a titre of less than 1000. On the other hand, none of the 5 patients who died who were given sulfapyridine and antigen or sulfapyridine alone showed a titre as high as 1,000,000 and 2 of them failed to show a titre as high as 1000.

Summarizing the mouse-protection studies, one may say that most of the patients recovering from pneumococcal pneumonia, except for Type III infections, show a high titre regardless of treatment. Less than half of the Type III cases showed any appreciable mouse-protective power. The largest percentage of high titres is seen in the serum-sulfapyridine treated group, of which Type VIII was strikingly lowest. Further, if Type III cases are excluded, the sulfapyridine-antigen treated cases showed a better response than those treated with sulfapyridine alone. Analysis of the deaths, however, indicates that the mouse-protective power is not a good prognostic sign, as a large percentage of the patients who die have a high protective titre.

The normal individuals who were given the polyvalent pneumococcus vaccine showed very little response in so far as the polysaccharide skin test was concerned. In all of the individuals, before

the vaccine was given, the test with the use of Type I and Type II specific polysaccharide was negative. In one individual the test against Type I became positive on the 8th day and remained so through the 15th day. Skin tests for Type II remained negative throughout. In a second individual the test with the Type I polysaccharide became positive on the 15th day but test with Type II remained negative. Thus 2 patients out of 10 developed a positive skin test against the specific polysaccharide of Type I only. None of the 10 developed a positive reaction with Type II.

The mouse protection titre of these normal individuals gave more suggestion of immune response to the vaccine. Before the administration of vaccine, 2 of the individuals showed a mouse protection titre of 10 M.L.D. In these 2 individuals, by the 15th day, the titre had risen to 10,000,000 or more M.L.D. Six of the remaining 8 who showed no protection before the administration of the vaccine developed titres of 10,000,000 M.L.D. or better within a 2-weeks' period. One individual developed a titre of only 1,000,000 M.L.D. and 1 had a titre on the 15th day of only 10,000 M.L.D.

Conclusions. 1. The type-specific polysaccharide skin test is a more reliable aid in the prognosis of pneumococcic pneumonia than the mouse-protective titre or the agglutinin concentration of the patient's serum, especially in those patients receiving adequate amounts of serum.

2. A limited number of observations indicated that the type-specific polysaccharide skin test is not passively transferred.

3. The combination of pneumococcus antigen with sulfapyridine resulted in a higher percentage of positive type-specific polysaccharide skin tests, in more positive agglutinin tests and in a higher mouse-protective power than were observed in the limited number of cases (12) when sulfapyridine was used alone.

4. Patients with Type III pneumonia are in a class distinct from others. The immune response as gauged by the tests in this study are not stimulated to the same degree as in other types of pneumococci.

5. Death occurs in certain cases in spite of apparently adequate antibody response, so far as can be determined by the observations as indicated above.

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SULFADIAZINE AND SULFATHIAZOLE IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA.

A PROGRESS REPORT ON 200 CASES.*

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ADVANCES in the chemical treatment of pneumonia have been occurring during the past 3 years at an ever-accelerating pace. To consolidate these advances and to evaluate the comparative merits of various chemotherapeutic agents it will be necessary to accumulate extensive data from different sources over a period of years. Of considerable interest would be data collected in a single hospital where the different compounds are being used. In previous papers[2,3,5,9] we have reported our clinical experiences with the use of sulfapyridine and sulfathiazole. At this time we wish to present our observations on the comparative therapeutic effectiveness and toxicity of sulfadiazine and sulfathiazole in the treatment of pneumonia.

Sulfadiazine,‡ 2-sulfanilamido pyrimidine, synthesized by Roblin *et al.*,[8] is the pyrimidine analogue of sulfapyridine. Its therapeutic effectiveness and toxicity in experimental animals has been investigated by Feinstone *et al.*,[1] who found that the drug had a high therapeutic activity against pneumococcal infection and caused less tissue damage than either sulfapyridine or sulfathiazole. The behavior of sulfadiazine in man has been reported by Plummer and Ensworth[6] and by us.[7] It was found that the drug is readily absorbed from the gastro-intestinal tract, is not excreted as readily as sulfathiazole, and disappears from the blood slowly. Sulfadiazine is readily secreted into peritoneal and pleural fluids with resultant concentrations approximating those in the blood. In cerebrospinal fluid, concentrations averaging 50% of the blood value were found.

* Aided by a grant from the American Philosophical Society.

† Detailed for this and related studies on pneumonia by the Pennsylvania Department of Health, Division of Penumonia Control.

‡ The sulfadiazine used in this study was supplied us by Dr. Howard Hogan, Nepera Chemical Company, Yonkers, N. Y.

Organization of the Study. A primary requirement in the evaluation of a new chemotherapeutic agent for pneumonia is to compare it with a proven form of therapy. Therefore, from the beginning of this study (November, 1940) the medical services* in the hospital were divided into two therapeutic groups, so that approximately half of the pneumonia patients received the new drug, sulfadiazine, while the other half served as controls and were given sulfathiazole. For this report we have taken the first 173 typed cases (87 sulfadiazine, 86 sulfathiazole) and, in addition, the first 13 non-typed sulfadiazine treated patients and the first 14 non-typed sulfathiazole treated patients.

The diagnosis of pneumonia was established by the clinical history and the findings on physical examination. When indicated, the diagnosis was confirmed by Roentgen studies. A specific pneumococcus type was recovered from the sputum or blood stream in 173 patients and in 27 the sputum failed to yield a type with pneumococcus serum Types I to XXXIII. Repeated blood counts and urinalyses, as well as blood cultures, were made in all patients. Determinations of free and total drug in the blood were made on all patients receiving either sulfadiazine or sulfathiazole. Special studies were performed on most of the daily urine samples for crystals of both drugs. Other laboratory procedures were carried out as indicated.

Dosage. The following dosage was employed: With sulfadiazine, an initial 3 gm. dose by mouth was followed by 1 gm. every 4 hours, unless signs of severe toxicity developed. Treatment was continued until the temperature remained normal for 48 hours, along with evidence of clinical improvement. With sulfathiazole, the dose schedule was the same as that used with the new drug, except that the first 3 gm. dose was repeated in 4 hours. This added quantity of sulfathiazole was used because previous experience has shown this to be an effective dosage.[5] In general, the total dosage was 25 to 35 gm., depending on the physical and laboratory findings in each case. The average total dosage for patients receiving sulfadiazine was 27 gm., as compared to 29.9 gm. for the sulfathiazole treated group. Type specific serum was administered when necessary. The indications for combined therapy cannot be specifically stated as each patient must be handled as an individual problem. In every instance that serum was used we were of the opinion that drug treatment alone was inadequate. It is our clinical judgment that additional therapy with specific serum is indicated in selected cases. Of the 200 patients included in this report, 18 (11 sulfadiazine, 7 sulfathiazole) received specific serum along with chemotherapy.

* Clinical facilities were given us for this study by the following Chiefs of Service: Doctors, R. S. Boles, C. L. Brown, H. D. Jump, Thomas Klein, D. W. Kramer, S. A. Loewenberg, W. E. Robertson, H. W. Schaffer, T. G. Schnabel, and the late R. G. Torrey.

In certain instances, where a rapid elevation of the blood level of either drug was desired, a 5% solution of the sodium salt of either drug (0.06 gm. per kilo of body weight) was administered intravenously as a supplement to oral therapy. The administration of 3 gm. of sulfadiazine sodium intravenously gave free blood levels of approximately 11.9 mg. per 100 cc. within 15 minutes. Furthermore, concentrations above 6 mg. per 100 cc. were readily maintained for at least 8 hours. Because of the slow excretion rate of sulfadiazine, the parenteral treatment of pneumonia appears to present practical possibilities. Further studies on this aspect of pneumonia therapy are in progress.

Therapeutic Results. In this report we have included all patients with a diagnosis of pneumonia who received drug therapy, except those with empyema or meningitis on admission. The results of treatment in the two therapeutic groups are shown in Table 1. Of

TABLE 1.—DISTRIBUTION OF TYPES, BACTERIEMIA, AND MORTALITY RATES.

	Sulfadiazine treated.				Sulfathiazole treated.			
	All cases.		Bacteriemic cases.		All cases.		Bacteriemic cases.	
Type.	No.	Died.	No.	Died.	No.	Died.	No.	Died.
I	15	1	7	1	14	..	3	..
II	3	..	..	..	2	..	1	..
III	15	4	3	2	18	7	3	3
Others	54	6	7	4	52	9	7	5
Non-typed	13	..	..	..	14	1	..	..
Total	100	11	17	7	100	17	14	8
Mortality, %	11.0		41.2		17.0		57.1	
Corrected mortality, %*	6.3		23.1		11.5		33.3	

the patients treated with sulfadiazine, 11 died (Table 2). In the sulfathiazole treated group there were 17 deaths (Table 2). Patients who were moribund on admission and died within 24 hours were included, although they did not provide a fair trial for either drug. Five such patients were treated with sulfadiazine and 8 with sulfathiazole. If these cases are excluded, the corrected mortality becomes 6.3% and 11.5% respectively for the sulfadiazine and sulfathiazole treated groups. Seventeen patients with bacteriemia were treated with sulfadiazine and 7 of these died (41.2% mortality). If the 4 bacteriemia patients, dying within 24 hours, are excluded, the corrected mortality in this sub-group is 23.1%. In the sulfathiazole treated group, 8 of the 14 bacteriemia patients died, and if the 5 24-hour cases are excluded, the corrected mortality becomes 33.3%.

In general, the distribution of race, sex (Table 3), age (Table 4), and day of disease on which treatment was begun (Table 5) were comparable in the two therapeutic groups. Although the number

* Does not include 13 patients (5 sulfadiazine, 8 sulfathiazole) who died in less than 24 hours after admission; 9 of these cases had bacteriemia (4 sulfadiazine, 5 sulfathiazole).

of cases is small, it is a striking fact that no sulfadiazine treated patients died when therapy was administered within the first 3 days of illness (Table 5).

TABLE 2.—ANALYSIS OF FATAL CASES.

No.	Age, yrs.	Day of disease treatment begun.	Type.	Blood culture.	No. of Lobes involved.	Total drug, gm.	Total serum, units.	Remarks.
				SULFADIAZINE.				
1*	59	14	I	Pos.	1	6	..	Moribund on adm., died in 12 hrs. Aut.: Lobar pneum., ac. supp. pericarditis.
2	60	7	III	Neg.	1	11	..	Asthma, card. decomp. No autopsy.
3	52	4	III	Pos.	3	40	100,000	Poor response to therapy. Sudden abd. catastrophe. Aut.: Perf. duod. ulcer, diffuse peritonitis, pul. abscess, resolving br.pneum.
4	72	8	III	Neg.	3	42	..	Responded well to therapy. Ready for discharge, sudden card. decomp. No aut.
5*	66	4	III	Pos.	1	7	..	Moribund on adm., died in 20 hrs. Asthma. No aut.
6	53	10	IV	Pos.	1	27	200,000	Toxic hepatitis (Ict. index 50 u.), card. decomp. on adm. No aut.
7*	60	8	IV	Pos.	2	7	..	Moribund on adm., died in 18 hrs. No aut.
8*	65	9	VI	Neg.	2	4	..	Chr. alcoholism, sudden death 22 hrs. after adm. Aut.: lob. pneum., degen. of liver, hypert. and dil. of heart.
9	76	4	XI	Pos.	2	28	..	Responded to therapy. Card. decomp. Azotemia (B.U.N. 65). No aut.
10*	38	4	XIV	Pos.	2	7	..	Moribund on adm., died in 20 hrs. Aut.: Lobar pneum.
11	47	5	XXIII	Neg.	2	41	100,000	No response to therapy. No autopsy.
				SULFATHIAZOLE.				
1	75	5	III	Neg.	3	47	100,000	Card. decomp. No autopsy.
2*	48	9	III	Pos.	3	7	..	Moribund on adm., died in 14 hrs. Aut.: Lobar pneum.
3*	60	7	III	Neg.	3	7	100,000	Moribund on adm., died in 12 hrs. Aut : Lob. pneum.
4*	67	5	III	Neg.	1	6	..	Pulm. tuberculosis, died 6 hrs. after adm. No aut.
5	67	10	III	Neg.	2	21	..	Cardiac failure, azotemia on adm. (B.U.N. 44). No aut.
6	59	5	III	Pos.	3	12	30,000	Serum sensitive. Over 1000 colonies per cc. blood. Aut.: Lob. pneum.
7*	39	4	III	Pos.	1	6	100,000	Moribund on adm., died in 10 hrs. Rheumatic ht. dis. Hypert., bl. pr.: 200/120. Azotemia (B.U.N. 85). Aut.: Lob. pneum., card. hypert., mitr. and aor. lesions.
8*	60	7	IV	Pos.	1	6	..	Moribund on adm., died in 12 hrs. Chr. alcoholism. Aut.: Lob. pneum.
9*	19	5	IV	Pos.	5	8	..	Moribund on adm., with leukopenia (2000 lcts.). Died in 12 hrs. Aut.: Lob. pneum.
10	74	9	IV	Pos.	2	22	..	Luetic ht. dis. with failure. Azotemia (B.U.N. 70) on adm. No aut.
11	52	4	VI	Neg.	2	10	..	Severe diabetes mellitus, ac. cor. occlusion, died in 36 hrs. No autopsy.
12*	27	3	VII	Neg.	1	7	..	Delirium tremens. Died in 14 hrs. after adm. Aut.: Lob. pneum.
13	40	5	IX	Neg.	4	8	..	Moribund on adm., died in 30 hrs. Aut.: Lob. pneum.
14	60	11	XVII	Neg.	2	8	..	Severe asthma, died in 32 hrs. No aut.
15*	44	7	XVII	Pos.	3	3	..	Moribund on adm., died in 8 hrs. Aut.: Lob. pneum.
16	59	3	XVIII	Pos.	3	20	100,000	Azotemia (B.U.N. 145), leukopenia (4000 lcts.) on adm. No autopsy.
17	65	1	..	..	1	27	..	Responded well to treatment. Cerebral thrombosis 23 days before adm. Aut.: bronchopneum., thrombosis of cerebral and cor. arteries.

* Patient died within 24 hours after admission.

TABLE 3.—MORTALITY ACCORDING TO RACE AND SEX.

Race.	Sex.	Sulfadiazine treated.		Sulfathiazole treated.	
		No.	Died.	No.	Died.
White	Male	39	8	28	7
	Female	11	1	18	2
Negro	Male	38	2	33	7
	Female	12	..	21	1

TABLE 4.—MORTALITY ACCORDING TO AGE GROUPS.

Age group, years.	Sulfadiazine treated.		Sulfathiazole treated.	
	No.	Died.	No.	Died.
12–19	8	..	4	1
20–29	17	..	17	1
30–39	25	1	20	1
40–49	17	1	23	3
50–59	12	3	22	3
60–69	16	4	9	6
70 and over	5	2	5	2

TABLE 5.—MORTALITY IN RELATION TO DAY OF DISEASE ON WHICH TREATMENT WAS BEGUN.

Day of disease treatment started.	Sulfadiazine treated.			Sulfathiazole treated.		
	No.		Died.	No.		Died.
1	9		..	8		1
2	14	61%	..	19	56%	..
3	24		..	18		2
4	14		4	11		2
5	14		1	14		5
6	8	39%	..	8	44%	..
7	8		1	13		3
7+	9		5	9		4

Influence of Treatment on the Course of the Disease. In evaluating any therapeutic agent, one must consider the effect of the agent on the course of the disease, as well as its influence on the mortality incidence. As shown in Table 6, a critical drop in temperature occurred within 24 hours in 66.3% of the patients treated with sulfadiazine as compared to 60.2% of the patients in the sulfathiazole treated group. At the end of 48 hours 87.6% of the patients in the sulfathiazole treated group. At the end of 48 hours, 87.6% of the patients receiving sulfadiazine showed a critical drop in temperature compared with 74.7% of the patients treated with sulfathiazole. The temperature fell to normal within 24 hours in 23.6% of the patients in the sulfadiazine treated group and in 15.7% of the patients receiving sulfathiazole. Within 48 hours normal temperature occurred in 61.8% and 44.6% of patients in the sulfadiazine and sulfathiazole groups, respectively. A secondary rise in temperature occurred in 10 patients (6 sulfadiazine, 4 sulfathiazole) and these usually required further drug therapy. Cases in which a diagnosis of drug fever was made are not included in this group. The average number of hospital days for patients in each therapeutic group is practically the same (13.6 days sulfadiazine, 13.3 days sulfathiazole). Not included in the latter group are all deaths and patients who remained in the hospital for various associated conditions (empyema, paresis, diabetes mellitus, heart disease, and so on).

TABLE 6.—EFFECT OF TREATMENT ON TEMPERATURE AND HOSPITAL STAY.

	Sulfadiazine treated.			Sulfathiazole treated.		
	No.	%.		No.	%.	
Critical fall in temperature:*						
Within 24 hours	59	66.3	87.6	50	60.2	74.7
Within 48 hours	19	21.3		12	14.5	
Within 72 hours	..	..		8	9.6	
Over 72 hours	11	12.4		13	15.7	
Temperature at normal level:*						
Within 24 hours	21	23.6	61.8	13	15.7	44.6
Within 48 hours	34	38.2		24	28.9	
Within 72 hours	13	14.6		14	16.9	
Over 72 hours	21	23.6		32	38.5	
Secondary rise in temperature (above 99° F.)*	6			4		
Average stay in hospital	13.6 days			13.3 days		

* All deaths excluded.

Not included in this group are all deaths and patients kept in hospital for further study and treatment of accompanying conditions.

Complications. The incidence of complications was low and little different in the two therapeutic groups. Empyema developed in 2 cases, 1 with each drug; both patients recovered. Massive pleural effusion occurred in 5 cases (3 sulfadiazine, 2 sulfathiazole) with no deaths. The diagnosis of lung abscess was made in 2 patients receiving sulfadiazine, with 1 death.

Toxic Reactions. In this series of 200 patients the incidence and severity of toxic reactions was comparable for the two therapeutic groups. Nausea and vomiting was mild and infrequent in both groups. In only 1 instance was it necessary to stop drug therapy because of severe vomiting and this occurred in a sulfadiazine treated patient who also developed a skin rash.

TABLE 7.—INCIDENCE OF TOXIC REACTIONS (200 CASES).

Toxic reactions.	Sulfadiazine treated (incidence, %).	Sulfathiazole treated (incidence, %).
Nausea	10.0	21.0
Vomiting:* Mild	4.0	8.0
Moderate	..	1.0
Severe	1.0	..
Total	5.0	9.0
Hematuria—microscopic	4.0	9.0
Dermatitis	1.0	2.0
Conjunctivitis	..	1.0
Psychosis?	7.0	3.0
Drug fever?	1.0	2.0
Leukopenia (below 5000 W.B.C.)	2.0	2.0
Neutropenia (below 40% P.M.N.)	..	1.0

* Mild—less than three times; moderate—three or more times; severe—necessitated stopping the drug.

Microscopic hematuria was encountered in 4 patients receiving sulfadiazine and in 9 patients treated with sulfathiazole. Gross hematuria was not observed with either drug. In most instances daily examination of urine sediment was made especially for evidence of drug crystals. Approximately 29% of the sulfadiazine treated patients had urinary crystals as compared to 70% of those receiving sulfathiazole. Furthermore, sulfadiazine treated patients usually

had a smaller number of crystals in the individual specimens examined. A study is being made on the possible effect of alkalinization on the solubility of sulfonamide crystals in the urine. From preliminary observations it appears that all patients should receive alkalies with either drug.

Dermatitis, apparently caused by the administration of these drugs, was noted in 1 patient (morbilliform rash) in the sulfadiazine group and in 2 (1 maculopapular, 1 urticarial) receiving sulfathiazole. One patient in the latter group showed a mild conjunctivitis associated with the dermatitis.

The diagnosis of psychosis as being due to the use of chemical agents is difficult to establish. However, we have encountered 10 patients (7 sulfadiazine, 3 sulfathiazole) whose cerebral symptoms were attributed by us to the drug. Although it is too early to draw any definite conclusions regarding this toxic manifestation, it appears to us that sulfadiazine tends to produce cerebral symptoms more often than sulfathiazole. The question of drug fever is also difficult to evaluate in pneumonia, although 3 patients (1 sulfadiazine, 2 sulfathiazole) developed this condition.

Repeated blood studies* showed little evidence of a marked reduction in hemoglobin, red blood cell or white blood cell counts that could be attributed to either drug. In 4 patients (2 sulfadiazine, 2 sulfathiazole) the total white cell count fell below 5000, and in 1 sulfathiazole treated patient the percentage of neutrophils dropped to 32% after 6 days of treatment. All these patients recovered and in only 1 instance was treatment stopped. There were no cases of acute hemolytic anemia in either group, but, in view of the behavior of sulfadiazine in penetrating red blood cells,[7] such a possible complication should be anticipated.

Blood Concentrations of Sulfadiazine and Sulfathiazole. The average concentration of free sulfadiazine in whole blood[7] as shown by daily determinations during the entire period of treatment was 8.6 mg. per 100 cc., compared with an average concentration of free sulfathiazole in plasma[7] of 6 mg. per 100 cc. Under similar circumstances the average concentration of acetylsulfadiazine in whole blood was 1.7 mg. per 100 cc. as compared with an average concentration of acetylsulfathiazole in plasma of 2.3 mg. per 100 cc. The average proportion of total drug acetylated was 16.5% for sulfadiazine and 27.7% for sulfathiazole. These data on the different acetylation values for the two drugs are highly significant.

Comment. On the basis of mortality it appears that sulfadiazine and sulfathiazole are both effective drugs for the treatment of pneumococcic pneumonia. The mortality of 11% (corrected to 6.3%) in the sulfadiazine treated group and 17% (corrected to 11.5%) in the sulfathiazole group compare favorably when all of the factors

* Dr. W. J. Crocker, Chief of the Division of Clinical Pathology of the Laboratories of the Philadelphia General Hospital, coöperated with the authors in this phase of the work.

influencing fatality[4] are considered. As previously stated, no sulfadiazine treated patient died when therapy was instituted within 3 days of the onset of illness (Table 5). For both drugs the average mortality for this same time limit was 3.3%. Clinical response, as evidenced by a fall in temperature was slightly more striking with sulfadiazine than with sulfathiazole.

In both therapeutic groups there was a low incidence of serious toxicity from the use of these drugs. The relatively low incidence of vomiting in both groups is especially impressive when compared to our previous experience with sulfapyridine.[2,3,5] Microscopic hematuria was encountered more often in the patients receiving sulfathiazole and this, we believe, is related chiefly to two factors: (*a*) The more pronounced acetylation of the sulfathiazole molecule; and (*b*) the poorer solubility of acetylsulfathiazole in urine[1] as compared with acetylsulfadiazine. These two facts might readily account for a lessened irritation of the urinary tract by sulfadiazine and a consequent lowered incidence of microscopic hematuria. This impression is supported by our observation on the presence of fewer crystals in the urine of sulfadiazine treated patients.

Summary. 1. Sulfadiazine was given to 100 adult patients with pneumococcic pneumonia, and a control series of 100 patients was treated with sulfathiazole.

2. There were 11 deaths in the sulfadiazine series, 5 of which were hospitalized for less than 24 hours (corrected mortality for 95 patients, 6.3%). In the sulfathiazole series there were 17 deaths, 8 of which were hospitalized for less than 24 hours (corrected mortality, 11.5%).

3. Sulfadiazine tends to lower the temperature somewhat more rapidly than does sulfathiazole.

4. The toxic manifestations were approximately the same in the two therapeutic groups.

5. The group treated with sulfadiazine showed higher concentrations of free drug than did the group receiving equivalent amounts of sulfathiazole.

6. The average proportion of drug acetylated was 16.5% for sulfadiazine and 27.7% for sulfathiazole.

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BOOK REVIEWS AND NOTICES

HAEMORRHOIDS AND THEIR TREATMENT: The Varicose Syndrome of the Rectum. By KASPER BLOND, M.D., Vienna, Formerly First Assistant, Rothschild Hospital, Vienna; Hon. Consulting Surgeon, Municipal Hospital, Vienna, etc. Translated by E. STANLEY LEE, M.S., F.R.C.S., Hon. Assistant Surgeon, Westminster Hospital. Pp. 140. 49 illustrations, many in color. Baltimore: The Williams & Wilkins Company. 1940. Price, $4.50.

THIS book propounds the interesting point of view that such diseases of the anal and perianal region as hemorrhoids, pruritus, fissure, proctitis, fistula, prolapse of the rectal mucosa are all due to what he terms "a varicose syndrome of the rectum." By this he means that there is a temporary reversal of flow in the portal circulation which permits the portal blood to flow through the superior, middle and inferior hemorrhoidals to the caval circulation. This he believes is the cause of the anorectal varices which secondarily are the cause of the various lesions and diseases of this area. In the treatment of these lesions, he recommends an injection method that he terms "vein-compression." The injections are made in small doses, 1 to 2 minims in a succession of circles beginning 8 to 10 cc. above the anorectal line. He uses quinine bihydrochloride and urethane and does not attempt to thrombose vessels but simply to set up an inflammatory reaction, which will compress the superior hemorrhoidal veins and so cut off the back flow from the portal into the caval circulation.

The author recognizes that for thrombosed external hemorrhoids surgery is necessary, but anal fissures, which he describes as varicose ulcers of the anus, he injects with 1 or 2 drops of quinine-urethane solution at the base after a topical application of cocaine.

He looks upon anorectal fistula as a suppurative thrombo-phlebitis of the anorectal veins and treats these lesions also by vein compression. He believes that thrombophlebitis of the anorectal area may be the cause of many types of biliary disease and devotes a chapter to the discussion of this subject.

Although the ideas expressed and the therapies suggested differ from those in general usage, nevertheless the subject and its presentation are most interesting, especially to one interested in proctology. L. F.

THE 1940 YEAR BOOK OF PATHOLOGY AND IMMUNOLOGY. Pathology. Edited by HOWARD T. KARSNER, M.D., Professor of Pathology; Director of the Institute of Pathology, Western Reserve University, Cleveland. Immunology. Edited by SANFORD B. HOOKER, A.M., M.D., Professor of Immunology, Boston University School of Medicine; Immunologist, Massachusetts Memorial Hospitals. Pp. 688; 115 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, $3.00.

FOR some years past, physiologists and biochemists have greatly profited by the Annual Reviews of their specialties. Pathologists and immunologists have long wished for a similar annual survey of progress, and the present Year Book represents realization of their wish. Ably edited by two well-known authorities, this book will find a ready welcome. The section on pathology (pp. 1–365) deals with recent progress in general pathology, with the pathology of tumors, the pathology of the various systems of

organs, and with advances in technical methods. The chief subjects reviewed in the section of immunology (pp. 383–653) are: immunity to bacterial diseases, to viral and rickettsial diseases, to protozoa, and to tumors; there are chapters on chemotherapy, anaphylaxis and allergy, blood groups, and immunochemistry. Since pathology and immunology are basic sciences of interest to every discipline of medicine and surgery, this year book may be expected to be of great interest to others than pathologists and immunologists. The editors and publishers are to be congratulated on launching this useful work. B. L.

CLINICAL ROENTGENOLOGY OF THE ALIMENTARY TRACT. By JACOB BUCKSTEIN, M.D., Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York City; Consultant in Gastro-Enterology, Central Islip Hospital. Pp. 652; 525 illustrations. Philadelphia, W. B. Saunders Company, 1940. Price, $10.00.

THIS book consists of 58 chapters in which the alimentary tract, gall bladder and bile ducts, diaphragm, spleen, liver and pancreas are discussed in detail. The author has consulted most of the important literature and has discussed and illustrated many of the lesions involving those portions of the intestinal tract in which he was interested. The illustrations, published in the negative, are exceedingly good. The author has allotted more space to the small intestines than is found in any of the recent books on the gastro-intestinal tract. For this he is to be complimented as the small intestines have been largely overlooked by clinicians, gastro-enterologists and radiologists. There is still much to be learned about this portion of the gastro-intestinal tract.

This Reviewer was a little surprised that the author did not stress a standard meal more than he has, as a standard meal seems essential if radiologists are going to compare their studies. Furthermore, subjects like gastro-intestinal allergy and vitamin deficiency and physiologic motility cannot be adequately determined unless standard meals, containing no food elements or preparations facilitating suspension of the barium are used.

The Reviewer was also disappointed in not finding more discussion of the determination of tone in the unfilled stomach, and of the problem of non-opaque gastric residues in the stomach which shows slight or no delay of gastric motility. The Reviewer was also a little surprised that more consideration had not been given to the method of studying intestinal obstruction devised by T. Grier Miller and W. O. Abbott—one of the really important contributions to medicine of recent years.

In spite of the above comments this book is a distinct addition to our knowledge of these subjects and the author has done a magnificent piece of work. His subject matter has been arranged in a perfectly logical manner and the publishers have given him a good paper on which the print stands out well and the paper is not too glossy. This book should be an acceptible addition to the libraries of clinicians, gastro-enterologists and radiologists.
E. P.

HYDROCEPHALUS. Its Symptomatology, Pathology, Pathogenesis and Treatment. By OTTO MARBURG, M.D. Pp. 217; 28 illustrations. New York, Oskar Piest, 1940. Price, $3.00.

HERE is brought together such important literature as already exists, to which is added the author's personal experience. It is believed hydrocephalus results from disturbance of water metabolism, the ventricles are enlarged, communications obstructed and in this way the disease is produced. Treatment must be directed toward changing the permeability of the blood-vessel walls and the barriers, and of the water metabolism. Important chapters are Etiology and Occurrence, Symptomatology and Syndromes, and Treatment. The last includes healing *per se*, medical

treatment, *x*-ray treatment, spinal puncture, cisternal and ventricular puncture, lasting drainage—callosal puncture, plexectomy, ligature of the carotids and decompressive trepanation. This is an interesting monograph; after reading it one has the impression that the treatment of hydrocephalus is still to be largely experimental. The bibliography covers 24 pages.

N. Y.

MAN'S GREATEST VICTORY OVER TUBERCULOSIS. By J. ARTHUR MYERS, Ph.D., M.D., F.A.C.P., Professor of Medicine and Preventive Medicine and Public Health, University of Minnesota, and Chief of Medical Staff, Lymanhurst Health Center, Minneapolis. Pp. 419; 31 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $5.00.

DR. MYERS has written a book for the veterinary medical profession on the control of tuberculosis in cattle, but with the perfectly obvious secondary if not actually primary aim of inspiring physicians and public health officers, through the example afforded, to renewed effort for the conquest of tuberculosis in man. In constructing the volume he has not felt bound by the title to limit its contents strictly to the subject of bovine tuberculosis, but has allowed himself wide latitude for the discussion of other triumphs of veterinarians and for much general information on tuberculosis in man. All of this adds to the value of the book. The veterinarian will find it an uncommonly successful source book for ready reference on the half century of bovine tuberculosis control, and will find it almost equally useful for technical information on tuberculosis. A unique feature is the assemblage of a series of short, biographical sketches of the lives of the veterinarians who have played a part in tuberculosis control.

In one sense it is a historical volume, but it uses the historical method as an object lesson rather than as an end in itself. The early successes and many early shortcomings and failures in tuberculosis control are noted at length; but the historical account leads quite directly to a detailed presentation of the existing bovine antituberculosis program. The drive in earnest, with eradication not mere control as an objective, began in 1917. The campaign of the Bureau of Animal Industry was simple in theory, although harassed by many difficulties in practice. Chapter XXII gives an inspiring picture of the persistence of the Bureau chiefs, and the final "accrediting" of the 48 states.

As in Dr. Myers' other books, each chapter ends with a concise summary. The method affords the reader a quick view of the entire subject. The summaries are concise and highly informative. The book is well illustrated and the press work is excellent.

E. L.

PSYCHIATRIC SOCIAL WORK. By LOIS MEREDITH FRENCH, Director, Study of Trends, American Association of Psychiatric Social Workers; Psychiatric Social Worker and Instructor in Mental Hygiene, New Jersey State Teachers College at Newark. Pp. 344. New York: The Commonwealth Fund, 1940. Price, $2.25.

IN this pioneer volume by Mrs. French, the effort is to describe psychiatric social work, what its workers do, and the relation it bears to psychiatrists, social agencies and the community. The present organization had its incipiency in 1920, and today there are about 500 members. It has served under different names and its future is somewhat uncertain. In 1935, 46% of its members were working in agencies that were a combined psychiatric and social service; in 1936, the percentage was 49; in 1937, 54; and in 1940, approximately 50%, thus receding to that of 14 years ago.

On 13 scattered pages there are attempts at definition of this work, and on 8 other pages, the difficulties attending such definition are mentioned. Where the service operates in general hospitals with an associated psy-

chiatric clinic, it operates efficiently; but where the effort is a study of emotional problems that may be found in any clinic, conflict arises between the psychiatric and medical approach. A bibliography of 14 pages and a helpful index are included. N. Y.

THE ENDOCRINE FUNCTION OF IODINE. By WILLIAM THOMAS SALTER, Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Laboratory, Boston City Hospital. Pp. 351; 40 figures and 45 tables. Cambridge, Mass.: Harvard University Press, 1940. Price, $3.50.

THIS is an admirable survey, containing a wealth of data from the literature and from the author's investigations, and analyzed with critical discernment. It includes discussions of iodine balance and endocrine balance, "labeled" radioactive iodine in the study of thyroid function, iodine in relation to endocrine glands other than the thyroid, clinical problems of iodine medication in thyroid disease, laboratory methods, and many other problems of iodine metabolism and thyroid function. The author puts various isolated facts into relationship to each other, and makes of these separate findings a reasonable whole. He writes in a delightfully readable style. Undoubtedly this book will be enthusiastically read by both investigators and practising physicians. I. Z.

RELATION OF TRAUMA TO NEW GROWTHS. Medico-Legal Aspects. By R. J. BEHAN, M.D., Dr. Med. (Berlin), F.A.C.S., Surgeon, St. Joseph's Hospital and Dispensary, City of Pittsburgh Hospital at Mayview, The Tuberculosis Hospital at Leech Farm, and the Allegheny County Hospital at Woodville. Pp. 425. Baltimore: The Williams & Wilkins Company, 1939. Price, $5.00.

ANY expert who is called upon to express an opinion regarding the rate of trauma as related to the onset of malignancy must be acquainted with this book. It is an essential addition to the library of surgeon, orthopedist and pathologist. G. W.

IMMUNE-BLOOD THERAPY OF TUBERCULOSIS. With Special References to Latent and Masked Tuberculosis. By JOSEPH HOLLOS, M.D. Pp. 195. Boston: Bruce Humphries, Inc., 1938. Price, $2.50.

CAREFUL perusal of this book leaves the Reviewer interested but skeptical. H. H.

STUDIES FROM THE CENTER FOR RESEARCH IN CHILD HEALTH AND DEVELOPMENT, SCHOOL OF PUBLIC HEALTH, HARVARD UNIVERSITY. (Monographs of the Society for Research in Child Development.) Washington, D. C.: Society for Research in Child Development, National Research Council, 1939.

TYPES, LEVELS, AND IRREGULARITIES OF RESPONSE TO A NURSERY SCHOOL SITUATION OF FORTY CHILDREN OBSERVED WITH SPECIAL REFERENCE TO THE HOME ENVIRONMENT. (Vol. IV, No. 2, Serial No. 21, Price, $1.25.) By ELEANOR SLATER, with the assistance of RUTH BECKWITH and LUCILLE BEHNKE. Pp. 148; 7 illustrations and 15 tables.

IN the course of a comprehensive study of child development which is in progress at the Harvard School of Public Health, the reactions of 40 children to life at a nursery school were studied. The number of changes in play, the number of contacts with other children, and of contacts with adults, the number of words spoken in 125 minute periods and various other aspects of behavior which could be recorded objectively were studied. A study of these factors from day to day showed definite trends. Some of the children were more inhibited at the beginning, some were accelerated at first and some fluctuating. One of the most interesting observations was that

the upper third of the group according to intelligence tests were the most inhibited upon entering the school.

An attempt was made in 13 cases to examine the behavior in the nursery with reference to home conditions. Changing conditions at home were associated in many instances with marked irregularities in the responses observed in the nursery. The authors however state that "a small child is subject to too many stresses both outside and within himself to make one able to isolate any one factor as primarily responsible for any changes in behavior or symmetry of development."

THE PHYSICAL AND MENTAL GROWTH OF GIRLS AND BOYS AGE SIX TO NINETEEN IN RELATION TO AGE AT MAXIMUM GROWTH. (Vol. IV, No. 3, Serial No. 22, Price, $2.00). By FRANK K. SHUTTLEWORTH. Pp. 291; 150 illustrations and 110 tables.

ON the basis of data collected on 747 girls and 711 boys under the direction of Professor Walter F. Dearborn, the author has presented detailed analysis—152 graphs and 110 tables—of 9 dimensions, erupted teeth and intelligence test data in relation to "MG-age" or age at the close of the year of maximum growth in standing height. This classification provides an interesting method of grouping individuals with similar patterns of physical growth, probably due to the timing of underlying endocrine factors, since a previous study had shown a high correlation between menarcheal age and age at maximum growth in standing height.

He has found that early MG-age groups are consistently bigger than the late MG-age groups up to the age of 12 for girls and 14 or 15 for boys, but that these differences tend to disappear or are reversed at later ages. When growth curves are plotted not to chronological age but arranged with significant points in the same vertical line, the slopes of the different groups are similar although differing in intensity, and the slope for each dimension has its own characteristics. Early MG-age groups attained their 28 teeth a little sooner and are found by intelligence tests to be brighter than the late MG-age groups. In concluding, the author postulates a theory of physical growth emphasizing the influence of hereditary stature factors in cancelling the differences created by variation in the timing of endocrine stimulation.

This is probably the most complete study of the subject ever published and furnishes a tremendous amount of reference material for those who are studying the growth of children.

EVALUATIONS OF ADOLESCENT PERSONALITY BY ADOLESCENTS. (Vol. IV, No. 4, Serial No. 23, Price, $1.00.) By CAROLINE MCCANN TRYON. Pp. 83; 12 illustrations and 15 tables.

To discover qualities or aspects of personality which children consider desirable in each other, 350 children in the high sixth and low seventh grades of Oakland public schools, whose average age was 12 years, were given booklets with 20 pairs of attributes (*e. g.*, restless and quiet, leader and follower, and so forth) and asked to write down the names of their classmates who seemed to be described. Three years later the same group in the high ninth grade were given the same tests, when their average age was 15 years.

The material obtained has been analyzed statistically and the graphic presentation of correlation profiles shows clearly the close relationship of certain traits: such as "popular, good-looking, friendly, enthusiastic" for the 15 year old boys. It is shown that values for boys change little from the age of 12 to 15 years with prestige being determined by physical skill, aggressiveness and fearlessness, although being unkempt becomes an undesirable characteristic of older boys. Changes for the girls are more marked "with emphasis shifting from being lady-like and conforming with adult standards to being a good sport and attractive to boys."

This monograph furnishes many interesting glimpses into the thoughts of the adolescent. T. R.

NEW BOOKS.

The Therapy of the Neuroses and Psychoses. A Socio-Psycho-Biologic Analysis and Resynthesis. By SAMUEL HENRY KRAINES, M.D., Associate in Psychiatry, University of Illinois, College of Medicine; Assistant State Allienist, State of Illinois, etc. Pp. 512; 3 figures. Philadelphia: Lea & Febiger, 1941. Price, $5.50.

Radiology Physics. An Introductory Course for Medical or Premedical Students and for all Radiologists. By JOHN KELLOCK ROBERTSON, F.R.S.C., Professor of Physics, Queen's University, Kingston, Canada. Pp. 270; 188 illustrations. New York: D. Van Nostrand Company, Inc., 1941. Price, $3.50.

Age Morphology of Primary Tubercles. By HENRY C. SWEANY, M.D., Medical Director of Research, Municipal Tuberculosis Sanitarium, Chicago, and Research Associate, Department of Physiology, University of Chicago. Pp. 265; 75 plates and 26 charts. Springfield, Ill.: Charles C Thomas, 1941. Price, $5.00.

Debatable Tumours in Human and Animal Pathology. By W. F. HARVEY, E. K. DAWSON, and J. R. M. INNES. From the Research Laboratory of the Royal College of Physicians, Edinburgh, The Cancer Control Organization of Edinburgh and South-East Scotland, and the Institute of Animal Pathology, University of Cambridge. (Cancer Research, Ltd., 1940.) Pp. 124; 40 plates. Edinburgh: Oliver & Boyd, Ltd., 1940, for the Cancer Control Organization of Edinburgh and South-East Scotland. Price, 10/6.

The American College of Physicians. Its First Quarter Century. By WILLIAM GERRY MORGAN, M.D., LL.D., Sc.D., M.A.C.P., Historian; Professor of Gastro-enterology and Emeritus Dean, Georgetown University School of Medicine, Washington, D. C. Pp. 275; illustrated. Philadelphia: American College of Physicians, 1940. Price, $2.00.

This is a valuable record of the first 25 years in the existence of an important medical organization, with particular interest for those especially concerned with its welfare. It gives a chronologic account of the existence of the College, biographic sketches of its important officers, and in the latter half of the book a "Chronology" extracted from the minutes of the College meetings.

Diseases Affecting the Vulva. By ELIZABETH HUNT, B.A., M.D., CH.B. (LIVERP.), Honorary Physician to the Skin Department, South London Hospital for Women; Honorary Dermatologist, New Sussex Hospital for Women and Children, Brighton, etc. Pp. 215; 36 illustrations and 18 plates in color. St. Louis: The C. V. Mosby Company, 1940. Price, $4.50.

The Journal of Clinical Endocrinology, Volume 1, No. 1, January, 1941. Issued Monthly for The Association for the Study of Internal Secretions. Pp. 90; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, Annual subscription, $6.50; single copies, $1.00.

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PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF

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OVARIAN TUMORS.

When one is confronted with an obvious ovarian tumor, it is of much help to have some statistical information as to the relative incidence of the various types of tumors, their symptomatology and probability of malignant change as can be analyzed from a large series of tumors of all types. In a study of 1101 ovarian tumors presented by Bernstein,[1] it was found that the simple and dermoid cysts were first and second in order of incidence. Papillary serous cancer was third, constituting 80% of all ovarian cancers and being four times more frequent than the benign serous cystadenoma. In this series, 17.3% of all ovarian tumors were malignant, 95% of these being cancer and 5% being sarcoma. Fifty-eight per cent of all ovarian tumors are in patients between 20 and 40 years, 30% are over 40 years and 12% under 20 years. Normal menses occur in over half of the patients with ovarian tumors, hyperfunctional bleeding in about one-quarter and hypofunctional bleeding in about 18%. In 58% of menopause patients malignancies were found, while metastases were noted at operation in 76% of the patients with ovarian cancer, 80% of these being due to papillary serous cystadenocarcinoma. Pain constitutes 44% of all symptoms and is present in 75% of the patients, but is usually not severe even in the late stages and is 25% more frequent among the benign tumor cases. Nausea and vomiting constitute only 19% of the complaints, being present most frequently in the benign tumor cases. Of all the cases there was bilateral involvement in 21%, but of the malignant cases alone the involvement was bilateral in 55%. In brief, therefore, when a patient past the menopause has a bilateral ovarian tumor which causes little pain, malignancy must be strongly suspected.

In order to understand how ovarian tumors are formed it is necessary to study the development of the ovary which has been well summarized by Geist[8] who reminds us that early in the development of the gonad the surface epithelium of the anlage of the ovary becomes many layered and extends downward into the mesenchyme as solid cell cords. This

represents the indifferent gonadal stage but rapidly passes into that of the definitive sex gland. In the male, the cell cords form the tubular system and possibly the interstitial cells, while in the female they become the undeveloped granulosa and theca interna cells, which later are utilized in the development of the Graafian follicle, although some recent observers believe that the granulosa and theca cells are derived from the mesenchyme. In addition to the two cell types mentioned, there remain in the female gonad remnants of structures that achieve full development only in the male and are identified as cords and tubules in the region of the rete ovarii. These structures usually remain quiescent but may develop and function in a male direction. Occasionally gonads are encountered that are functionally inefficient and may not develop either along male or female lines. With this brief preface we shall mention the four types of tumor which have been of so much interest of late, although each type will be considered in more detail later.

The granulosa cell tumor arises from unused granulosa cell forerunners in the ovary. These tumors store or produce estrogenic hormone and affect the host by exaggerating certain aspects of the female physiology.

The theca cell tumor arises from the forerunners of the theca interna cells and in their biologic aspect are similar to the granulosa cell tumor, but are commonly found in the postmenopausal period.

The arrhenoblastoma arises from male-directed elements which have remained quiescent in the ovary and presumably contain a male sex hormone. They affect the host by causing a defeminization with the development of a male hair type, male gait, voice and larynx.

The dysgerminoma arises from neuter cells of germinal epithelial origin. It has no incretory function and no pathologic physiologic effect on the host, but is found often in individuals with defective gonads and atypical somatic development.

Granulosa Cell Tumor. According to Schulze[17] the clinical picture of granulosa cell tumor is sufficiently definite to allow of preoperative diagnosis, particularly in the preadolescent and postmenopausal groups. The prognosis of these tumors cannot be considered settled as most of the cases in the literature are reported without adequate follow-up, and a number of cases of late recurrences have served to upset somewhat the former idea of a very low rate of malignancy in these tumors. The clinical picture of these tumors, aside from certain mechanical effects which might be due to any type of ovarian tumor, is due to excess estrogenic activity of the growth. In children, there is precocious puberty, in postmenopausal women, rejuvenation with a resumption of cyclic or irregular uterine bleeding, swelling of the breasts with occasional galactorrhea and restoration of a youthful type of vaginal mucosa. In the adult premenopausal woman, irregular, profuse and prolonged bleeding alternating with periods of amenorrhea is characteristic. A glandular cystic type of hyperplasia of the endometrium has been found in a high proportion of cases where it has been examined. Sterility is theoretically to be expected through inhibition of the pituitary and secondarily of the remaining ovary by the hyperestrinism produced by the tumor. One of Schulze's patients had been sterile for 5 years, yet delivered a normal child 2 years after operation without other treatment for the

sterility. The question of the radiosensitivity of granulosa-cell tumors is not settled. Most of the reports of inoperable, incompletely removed or recurrent tumors which have disappeared under Roentgen ray treatment have been made too soon to know what the final outcome will be. A recurrence of bleeding following adequate radiation treatment for supposed functional menorrhagia, however, should certainly warrant further study of the patient, bearing in mind the possibility that a small unrecognized granulosa-cell tumor might be present. In spite of the relatively high rate of malignancy reported in some series, Schulze believes that the proportion of cures in cases adequately followed is still very great unless there was definite evidence of malignancy at the time of operation and therefore conservative operation is indicated in young women, although they should be followed for a long time to guard against late recurrences.

Bland and Goldstein[2] are also of the opinion that these tumors are not very malignant. They have studied a series of 160 cases in 96 of which the final outcome is known; 42 were well for periods of from 1 to 10 years following operation, while 20 patients were dead, 4 of them dying from metastases within one year after operation. The same opinion is expressed by Dockerty and MacCarty[6a] of the Mayo Clinic where 30 of these tumors have been encountered including one that weighed 34 pounds. They have found that these tumors cause a hyperplasia of the uterus with a thick, boggy, proliferative type of endometrium often containing cysts. In their experience 90% of these tumors are unilateral, 90% are solid and 90% are of a low grade of malignancy. They are usually well encapsulated, the cut surface has the homogeneous, granular appearance of liver sausage which allows one to make a correct gross diagnosis in 50% of the cases. Of the 30 cases, 25 are living and well from 2 to 30 years after operation.

There has been considerable confusion in the differentiation of granulosa and theca cells in some instances, and Traut and Marchetti[19] state that such differentiation is never easy and in some cases may be impossible. However, they call attention to the fact that comparatively little work has been done with the aid of silver impregnation methods and they believe that the Foot silver stain has never been used in connection with granulosa and theca neoplasms. They state that this technique has many advantages. It not only reveals the argentaffine characteristics of reticular and cellular cytoplasm, but it also gives a finely graduated tonal differentiation of all the cells. Neoplastic granulosa cells occur in islands consisting of from a few to several hundred cells, seldom existing singly. These islands are surrounded by strands or networks of reticulum carrying with them numerous theca cells and the vascular supply. The nuclei of theca and granulosa cells are impossible to distinguish from one another, as they contain similar nucleolar and chromatin bodies. However, the cytoplasm of the granulosa cells contains many argentophile granules, whereas the cytoplasm of the theca cell is almost devoid of these bodies. In addition, the theca cell is always in intimate relationship to the reticular framework to such a degree that each cell is surrounded by a capsule of this material which isolates it from its neighboring theca cells. In contrast, the granulosa cells exist in groups, usually of large numbers, each cell being in immediate contact with its neighboring granulosa cells. The complete

island of granulosa cells is surrounded but not penetrated by the reticulum. The application of these differential points makes it possible to analyze the Graafian follicle tumors as to their content of these two types of cells. They state that so-called granulosa cell tumors contain varying amounts of theca cell elements as well, so that pure granulosa cell tumors are rare. Most tumors contain from one-fourth to one-third of their differentiated cells in the form of theca cells and, on the other hand, most so-called theca cell tumors also contain granulosa cell elements in considerable numbers.

Theca Cell Tumors. Since there have been reported only about 25 examples of this tumor it must be considered rare. In reporting a series of 10 cases Dockerty[5a] states that there are three theories to explain the origin of these tumors. In the first theory they are believed to be derived from the ovarian stroma and are regarded as luteinized fibromas. A second theory holds that they are luteinized granulosa cell tumors and that they should not be called "theca cell tumors." The third theory states that these tumors arise from theca cells and represent a separate entity. The clinical features usually associated with theca cell tumors resemble closely those found in association with granulosa cell tumors of the ovary. More than 80% of the neoplasms occur after the menopause and produce vaginal bleeding which may or may not be periodic, although some tumors produce no menstrual abnormalities. The tumors are fibrous, solid, usually encapsulated and canary yellow in color. On section, the "liver sausage" consistency of granulosa cell tumors is lacking and, except for the yellow color, a diagnosis of fibroma would seem justified on the basis of gross inspection. A thin "rind" of ovarian tissue can usually be shelled from the surface of the tumor in the form of a smooth capsule. Histologically, the cardinal features are the predominance of plump, fusiform cells with vacuolated cytoplasm and oval nuclei. It is generally conceded that they are of a low grade of malignancy.

Commenting upon these tumors, Collins, Varino and Weed[3] state that they vary in size from a few centimeters in diameter to the size of a large grapefruit. On vaginal examination the consistency is that of a fibroma of the ovary. The tumor is usually unilateral, may occur at any age, the oldest reported case being a woman of 90 and the youngest, 18 years old. All but 3 of the reported cases occurred at or past the menopause and are usually accompanied by atypical bleeding. In younger women, periods of amenorrhea, preceded or followed by menorrhagia, is the usual history. They believe that in the past many of these tumors have been reported as fibromas of the ovary. In the 2 cases which they have seen unilateral oöphorectomy was performed and, since removal of the tumors, normal menstrual cycles have been established in both cases.

Arrhenoblastoma. In contrast to the granulosa cell and theca cell tumors which have been described as feminizing, the arrhenoblastoma is a masculinizing tumor and it is quite a rare one, but like the other tumors previously described it is of a low grade of malignancy. Novak[14] states that this tumor occurs most frequently in relatively young patients, the decade between 20 and 30 showing the largest incidence. The defeminizing phenomena associated with this tumor consist of amenorrhea, retrogression of the mammary glands and loss of the femi-

nine contour, while the masculinizing effects consist of hirsutism, deepening of the voice and hypertrophy of the clitoris. Removal of the tumor is followed by a return to normality although this may not always be complete. Histologically, all gradations are seen between a structure closely simulating that of normal testis (testicular adenoma) to pictures showing only incomplete efforts at tubular formation, to those of sarcoma-like appearance. The rarity of the tumor may be judged from the fact that Dockerty and MacCarty[65] are able to present but 4 cases from the Mayo Clinic over a period of 26 years. They state that in the presence of a palpable pelvic tumor, associated with the masculinizing syndrome, a diagnosis of arrhenoblastoma seems justified. However, basophilic pituitary adenomas, pinealomas and adrenal cortical tumors may be associated with a similar clinical picture. Certain features help in distinguishing between them. Hypertension, a cardinal symptom of adrenal and pituitary neoplasms, is unusual in cases of arrhenoblastoma. A definite increase in weight with a "buffalo" distribution of fat is associated frequently with an adrenal or pituitary neoplasm but may occur with an ovarian tumor. Pituitary changes of a hyaline nature have been encountered in cases in which death has occurred owing to arrhenoblastoma, which leads them to ask whether or not this master gland may not be the basis of secondary sex changes. Granulosa cell tumors offer the only difficulty in making a differential diagnosis histologically. The pathologic characteristics of both tumors have a certain similarity but interstitial cells are absent in granulosa cell neoplasms and tubular structures are almost never observed. Malignancy in an arrhenoblastoma is shown by the usual criteria of multiple mitotic figures, irregularity in the size and staining properties of the nuclei and local invasion. It can be recognized in fresh sections of tumor tissue and, when present, warrants radical operation. Treatment, especially among younger individuals, should otherwise be conservative.

Dysgerminoma. The term "dysgerminoma" refers to a rare type of ovarian tumor which had formerly been called by a variety of names such as seminoma, embryoma, sex cell carcinoma and large round cell carcinoma. In presenting a paper which reviews 79 cases collected from the literature, Seegar[18] states that there are several clinical features which aid in arriving at a preoperative diagnosis of dysgerminoma, particularly the duration of symptoms and the age and sexual development of the patient. The occurrence of a large solid tumor in the ovarian region in a girl past puberty is suggestive of such a diagnosis. The duration of abdominal pain and swelling which are the principal symptoms, is usually about 6 months. There is a frequent association of this tumor with pseudohermaphroditism, hypogenitalism and other forms of sexual maldevelopment, such as infantilism, amenorrhea, delayed onset of menstruation and sterility, but the absence of such abnormalities is of no diagnostic significance. Extensive infiltration of the rectum or the bladder with involvement of the retroperitoneal lymph nodes occurs with the more malignant tumors, but metastasis to other organs is rare. The outstanding gross pathologic features of this tumor are the firm or elastic consistency, the nodular surface and the large size, often in excess of 2000 gm., suggesting rapid growth. The cut surface is granular and glistening and the more dense stroma-

togenous areas are widely separated. Microscopically, the cells of the tumor stand out individually, suggesting the appearance of caviar, especially in the frozen section. The cells are large and discrete and are arranged in nests and strands, with a moderate amount of clear cytoplasm which takes the eosin stain and with large hyperchromatic nuclei. One of the more constant characteristics of the microscopic structure is the lymphoid infiltration of the stroma. In Seegar's experience the degree of microscopic differentiation cannot be relied on in distinguishing a benign from a malignant tumor, and similarly the appearance of gonadotropic substance in the urine is unreliable as a guide to prognosis because of the scarcity of such determinations to date. Of the cases in this series in which there were adequate follow-up data, approximately 50% have remained well beyond 5 years. The treatment of choice for dysgerminoma is excision of the tumor, the uterus and the opposite ovary being left intact. The preservation of the child-bearing function is desirable for the patients, who are usually young adults. For patients showing hermaphroditism or sexual underdevelopment the possibility of future pregnancy is usually of no importance. For patients showing a recurrence of the tumor in the regional lymph nodes after a primary excision, irradiation or a second excision is indicated. Only 2 cases have been recorded in which a recurrence has occurred in the remaining ovary, while in 6 cases in which only the affected ovary was removed, the patient subsequently gave birth to a healthy child. This would seem to warrant the slight risk of recurrence in the opposite ovary which is assumed when conservative excision is practiced.

Commenting upon these tumors, Novak and Gray[15] state that since they arise from cells dating back to the undifferentiated phase of gonadal development, it is not surprising that an exactly similar tumor, the well-known seminoma, occurs in the testis. Moreover, since it is made up of sexually indifferent cells, the dysgerminoma exhibits no endocrine activity, thus differing from the feminizing granulosa cell tumor and the masculinizing arrhenoblastoma. While dysgerminoma is often observed in sexually underdeveloped or pseudohermaphroditic individuals, it has nothing to do with the production of these abnormalities, which persist even after the removal of the tumor. While the tumor is undoubtedly malignant, there are marked variations in the degree of malignancy of individual tumors. The outlook is very favorable when the tumor is unilateral with intact capsule, but much less favorable when the capsule has been broken through, with extensive infiltration of surrounding organs. They believe, therefore, that conservative unilateral operations should be limited to unilateral growths in which the capsule of the tumor is intact and in which there is no evidence of infiltration or metastasis, while in all other cases removal of both ovaries and uterus would seem preferable. In regard to the use of postoperative irradiation after a conservative unilateral operation, they advise against such a procedure, because such treatment, by destroying the function of the conserved ovary, is as radical as a complete operation in abolishing the reproductive function, the preservation of which is the chief justification of the conservative operation. If future reproduction is to be disregarded, the complete operation followed by radiotherapy would be safer and more desirable than unilateral removal plus radiotherapy.

Brenner Tumor. A rare ovarian tumor which was first described by Brenner in 1908 has been studied from the material available at the Mayo Clinic by Dockerty.[5b] These tumors resemble fibromas, but microscopically they contain scattered islands of pale-staining squamous epithelial cells in a dense stroma of connective tissue and Brenner called the tumor "oöphoroma folliculare." Three theories have been advanced to explain the formation of these tumors. According to the first theory (Robert Meyer) the neoplasm arises from metaplasia of the epithelium of the Muellerian ducts; the second theory (Schiller) postulates a dislocation of cells from the primitive urogenital connection, while the third theory holds that these tumors represent one-sided development of teratomas. The Brenner tumor is nearly always unilateral, varying in size from tiny nodules to masses 20 cm. in diameter. It resembles ovarian fibroma in being grayish-white and in the solid variety it is dense and hard. In another group, the tumor appears as a solid nodule growing from the wall of a cyst. Adhesions are infrequent and metastasis has not been observed. Microscopically, the picture consists of islands of squamous epithelial cells in a dense stroma of fibrous tissue. The peripheral rows of cells in these islands are frequently palisaded. Some are cystic with an inner lining of columnar cells and in some instances these cysts contain a substance which stains positively for mucus. Mitotic figures are not observed. The tumor must be distinguished from the granulosa cell tumor and also from metastatic squamous cell carcinoma, which is simple when the Galantha stain for mucus is employed. The clinical features of Brenner tumor are those of a slow growing pelvic tumor with none of the usual features of clinical malignancy. Sixty per cent of the neoplasms occur after the menopause. In discussing this study, Counseller[4] states that while the interest in these tumors is chiefly one of histogenesis, certain factors give it surgical importance. It is not a malignant tumor and has no effect on endocrine systems. It can be cured by unilateral removal of the adnexa but it must be distinguished from the other unusual neoplasms of the ovary such as granulosa cell tumor, arrhenoblastoma and dysgerminoma, in which the surgical treatment may not be the same. The identifying features in the gross appearance usually can be detected by the experienced gynecologist and the correct diagnosis made immediately from a frozen section. Panhysterectomy is not necessary to cure this tumor, but before the tumor became definitely established pathologically, panhysterectomy was the usual procedure since it was thought to be a malignant condition. Surgically, it is important to separate this tumor from metastatic lesions of the ovary since the prognosis and surgical procedure would vary considerably in the latter type.

Krukenberg Tumor. These interesting tumors are secondary to carcinoma elsewhere, usually in the gastro-intestinal tract. In their paper on this subject, Novak and Gray[15b] call attention to the false idea that some investigators have to the effect that all ovarian cancers secondary to gastro-intestinal cancer are Krukenberg tumors, but they insist that only those tumors, whether secondary or primary, which assume the characteristics first described by Krukenberg should be classified under this heading. The characteristics of the true Krukenberg tumor are, grossly, firm solid growths, usually of moderate size, almost always bilateral, and retaining the general shape of the ovary. The external

surface is smooth, with well developed firm capsule, with no tendency to become adherent to surrounding structures. On section some parts are quite firm, others finely spongy, some areas often degenerated, hemorrhagic or cystic, while areas of gelatinous appearance are common. Microscopically, the epithelial elements may occur as clusters of well marked acini showing various degrees of mucoid epithelial change which may be so extreme that the epithelial cells are completely melted down, leaving only the shadows of the original gland framework. The mucoid material may break through the gland wall and permeate the surrounding stroma, so that differential staining may reveal mucin not only in the glands but also in the stroma. The mucoid changes described explain the occurrence of usually large numbers of signet cells, in which the nucleus is flattened out against the cell wall by the accumulated secretion within the cell. It is these cells which have been most stressed in the microscopic diagnosis of these tumors, and which have suggested for them the designation of carcinoma mucocellulare. It would seem that this neoplastic type is brought about by the development of a primarily mucoid adenocarcinoma in the ovarian environment, or by the acquisition of mucifying tendencies by metastatic tumors which at their original site give no indication of mucoid characteristics. Such a course is not the invariable one pursued by gastro-intestinal cancers metastasizing to the ovary, since the great majority of such secondary growths develop as non-mucoid carcinomas, with the usual pattern of adenocarcinoma, so that they cannot properly be considered Krukenberg tumors. In view of the secondary character of this tumor, examination of the ovaries should never be omitted at operation for pyloric or other gastro-intestinal cancers in women. On the other hand, the gynecologist should explore the stomach and other abdominal viscera before proceeding with operations for ovarian cancer so that useless operations will be avoided. While the majority of these cancers are secondary, Novak and Gray believe that there is strong evidence for a primary origin in the occasional case, since in several cases reported the tumors were quite typical but there was no evidence at operation of a primary tumor elsewhere, none developed after the operation and the patients were in good health several years after operation. The prognosis in the common secondary cases is practically hopeless.

Concerning the frequency of these tumors, Kleine[10] of the gynecologic clinic at Heidelberg found that among 176 malignant tumors of the ovary observed over a 26-year period, 16% were Krukenberg tumors, which is distinctly higher than the usual percentage reported in the literature. There were 53 metastatic ovarian cancers but only 28 (53%) of these were of the Krukenberg variety with typical seal ring cells. No case of primary tumor was observed, all being secondary to cancer of the gastro-intestinal tract. In 88% of the cases the tumors were bilateral. The younger patients presented the largest tumors, up to the size of a man's head, while in patients at the menopause the tumors were usually small. In 60% of the patients there were menstrual symptoms, usually in the form of amenorrhea following destruction of the ovarian tissue.

Struma Ovarii. In discussing tumors of the ovary which contain thyroid tissue, known as struma ovarii, Emge[7] states that the histogenesis is obscure, but it is reasonably certain that they are not the

result of thyroid metastases into an ovary, since this is contrary to the behavior of metastasizing thyroid neoplasms. The actual incidence of these tumors is not known, but casual statistics place it at from 2 to 15% of ovarian teratomas, mainly dermoids. An ovarian struma, even though small, can unbalance the metabolism of the body and at times invade other tissues of the body by metastasis. Most of these tumors are silent unless mechanical difficulties arise and are usually not diagnosed until they reach the laboratory. They frequently come to operation without critical metabolic studies and milder types of hyperthyroidism are undoubtedly overlooked. Most ovarian strumas are benign tumors and are more common after maturity. When part of an ordinary teratoma they may not be encapsulated but may freely intermingle with other tissue. When encountered as a so-called pure struma they always have a capsule formed by mesoderm derivatives. Generally they tend to develop into a colloid goiter rather than to maintain hyperplastic activities. About 5% of these tumors may be expected to metastasize, usually to abdominal viscera.

Carcinoma. In reviewing over 100 cases of primary cancer of the ovary, Lynch[11] was struck by the insidious character of the disease. The first symptoms may be comparatively trivial and yet the tumor is found to be inoperable. When compelling symptoms are present, pain is the most common, usually mild at first, gradually increasing in severity. When the pain is epigastric, there is often nausea and vomiting. Menstrual disturbances are variable but may consist of postmenopausal bleeding. Of the 62 patients who were treated more than 5 years before the date of the study, there was a cure rate of 35% which should be gratifying, but Lynch is not at all satisfied after careful evaluation of the figures. Many of the patients have been re-operated or re-radiated during a period in which they should not be re-treated but merely observed. Furthermore, some of the slowly growing tumors that have been re-treated might have been still present but unrecognized on examination after 5 years, yet later they might develop and cause death. The cure rate depends largely upon the number of slowly growing tumors in the series and therefore he believes that it is useless to evaluate any method of treating ovarian cancer unless the patient has been followed for a minimum of 10 years from the date of the last treatment. He believes that the profession credits too many cures to the Roentgen ray. While this agent has been helpful in a considerable number of advanced cases, causing a rapid shrinking of the growth and decrease in the amount of fluid, there are as many cases that do not respond at all. He believes that if a patient remains well 5 or more years after the removal of a tumor with subsequent Roentgen ray treatment, the important factor in the cure is not as likely to be the irradiation as the complete removal of a cancer of low malignancy.

Based upon his analysis of 149 cases of primary ovarian cancer, Pemberton[16] is of the opinion that the uterus and both tubes and ovaries should be removed whenever possible, because bilateral growths occur so often and metastases are frequently in the back of the uterus. However, he realizes that it is often difficult and possibly useless to attempt this when the pelvis is filled with the growth and adherent omentum and intestine. The tumor should be removed intact if possible, while tapping, to decrease its size for easier removal, should be

reserved for elderly patients and poor risks. He advises removal of the omentum, regardless whether or not gross metastases can be seen in it, because it is so often affected and may be the source of recurrences later. The peritoneoscope is useful in discovering the extent of the disease. Since such a large percentage (47%) die within the first 2 years after operation, it might save a patient a useless operation and convalescence if she were not operated upon if the peritoneoscope showed generalized metastases throughout the abdomen. One cannot advocate no treatment, however, because such patients have nothing to lose and operation may prolong life in a few.

At the Massachusetts General Hospital over a period of 33 years only 16% of the patients with ovarian cancer survived the 5-year period according to Meigs.[12] The results of surgical treatment including the cases that had Roentgen ray therapy, show that in the solid and the solid and cystic group only 9% of the patients survived 5 years. In the more malignant group of papillary cysts about 23% survived 5 years. Inasmuch as many of these cysts looked fairly benign, the end results are appalling. There is no doubt that treatment by radiation following surgery is valuable, but although Roentgen ray treatment may slow the growth it does not cure. Roentgen ray treatment should be used in cases that have peritoneal extension, adhesions, whenever cyst fluid has been spilled, when a complete operation has not been done and in all cases in which there is any question as to the perfection of surgery. If a clean and complete excision has been done, radiation should not be used but should be withheld so that it may be used later if necessary. Although it is necessary to treat the entire abdomen, the usual procedure is to treat only two or three fields. This cannot adequately cover the entire abdomen, so that unless each field is marked off and treated, certain areas are sure to be missed. He states that it is the surgeon's duty to make a note of the location of the metastatic areas, where the adhesions were, and where the tumor has extended. These areas should be marked on an abdominal chart and sent to the Roentgen ray department when the patient is to be treated. The surgeon should discuss the lesion with the roentgenologist and decide where and how the tumor should be treated, and it is advisable to have the roentgenologist present at the operation so that he can see the exact location and extent of the tumor. Meigs found that 50% of the radiation group had solid cancer with 6.2% living 5 years without disease. This must be contrasted with 12.5% living in a similar group not radiated. In the malignant papillary cystadenoma group also, the patients not radiated did better than those who were radiated: 24% as against 18.7%. It is more hopeful to view the length of life in months of the patients having radiation, as compared to those not having it. In the solid tumors radiation prolonged life, 20.9 months as compared to 7.5 months; but in the cystic group life was slightly longer without it, 21.5 months as compared with 22.9 months. It is apparent from this study that no more people are cured with radiation than without it. It can be stated that cancer of the ovary is a very serious lesion and the solid type rates with the worst of all malignant tumors. If found early, cancer of the ovary is curable, for it is often encapsulated within the ovary and is not serious until the cyst is broken or perforated. Therefore early operation is essential in patients with questionable ovarian

lesions, since it is better to remove a simple cyst or a fibroid because of a mistaken diagnosis than to wait to see whether a given lesion becomes malignant. The preservation of ovarian tissue in women with ovarian cancer of papillary cysts, benign or malignant, is serious, and if this is done in order to allow pregnancy to occur, extreme caution must be exercised in the follow-up to guard against a growth in the other ovary.

A more optimistic note on radiation therapy has been sounded by Jacobs and Stenstrom.[9] From their experiences at the Cancer Institute of the University of Minnesota they believe that radiation will produce enough cures in carcinoma of the ovary, even when advanced, to make it a decidedly justifiable procedure. The amount of radiation must be adequate and repeated courses are probably advisable. They outline the technique that they have used which has given them a 5-year salvage of about 35%.

Fibroma. It has long been known that fibromas of the ovary are often associated with ascites, but now a new syndrome has been described by Meigs and Cass[13] in which, in addition to ascites, there is an associated hydrothorax. The importance of such a lesion seems great, for unexplained pleurisy with effusion and unexplained ascites are problems that occasionally confront internists and they should be aware that a benign ovarian tumor may be responsible for these conditions. On the other hand, a gynecologist who finds ascites and hydrothorax in a patient with a pelvic tumor might feel that malignancy was responsible for the conditions. It is important as well as encouraging to know that not only the ascites but also the hydrothorax may be cured by the removal of a benign ovarian fibroma, since such a patient might be doomed as inoperable under ordinary circumstances. The reason for the presence of fluid in the abdomen and chest in these cases is not clear. The ascites has been ascribed for many years to the irritation of the peritoneum by the hard tumor mass. It is possible that such irritation might cause abdominal fluid, but it does not seem possible to explain fluid in the chest by such reasoning. Both fluids seem to be part of the same process, since removal of the ovarian tumor causes both of them to disappear.

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DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF
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THE TRIVALENT ARSENICALS IN SYPHILIS.

SOME RECENT ADVANCES, COMPARISONS AND EVALUATIONS.

Some Theoretical Needs. In reviewing the arseno-therapy of syphilis it is always desirable to keep before one a species of chart of desiderata, and directions along which advance in knowledge and practice is urgently needed.

Stokes and Beerman[90] have summarized the points on which the clinical tester of drugs and the practising physician tend to query the introducers of the new arsenicals in the treatment of syphilis, as follows: *in the clinical testing:* (*a*) rapidity of surface spirillicidal action and healing power; (*b*) evidence of standard or reasonably rapid reversal of serologic tests in early syphilis; (*c*) a low incidence of relapse, infectious or otherwise; (*d*) a low incidence of involvement of the nervous system in early syphilis; (*e*) good effect on resistant syphilitic manifestations, and late syphilis of the important systems; (*f*) ultimate curative action in man; (*g*) a low incidence of reaction. *The practitioner desires to know:* (*a*) whether the drug will injure or alienate his patient by either minor or serious reaction; (*b*) is its administration so complicated as to constitute an *office* inconvenience; (*c*) will it cause rapid healing; (*d*) will it quickly relieve symptoms, especially pain; (*e*) what will it do for patients with a persistently positive serologic test on the blood. The sales campaigns are drawn primarily on the second group of criteria.

Increased "punch" whether expressed in greater efficacy of smaller doses, fewer injections for a given effect, shortened time for individual or total treatment, greater intensity made possible by lessened toxicity, are the experts' and the public health's first demands. *Lasting or staying power* is the second, and too little emphasized requirement, and one which must be seriously considered in drugs like arsenoxide (Mapharsen), in which a body of conservative opinion believes lack of this quality, real or imagined, to be a disqualification. *Stability and cheapness* are extremely important, since the latter can enormously increase availability, and the former, the spread and safety of handling. In a recent study of state practice, it was observed that the cost of arsenoxide had made impossible its use on a large scale, notwithstanding its obvious desirability in the types of cases under treatment. Stability, both under market conditions and in preparation for use at the hands of inexperienced physicians, has long been a serious shortcoming of neoarsphenamine, particularly troublesome because of its widespread use, and stability is rated a chief recommendation of Mapharsen and arsphenamine. Astonishing difficulties of technique and usability may be bridged or conditioned by this factor.

Simplification of the route of administration should constantly be striven for. Not only should a drug be acceptably and rationally introduced into the body, but questions of the rate of absorption, maintenance of blood and tissue concentration levels, storage and elimination for quick or prolonged effect must be considered. Intravenous therapy is, broadly speaking, an inferior rather than a superior procedure. Nothing more strikingly illustrates an unexpected aspect of such problems than the effect that the drugstore, as the source of the sulfonamides, an effective treatment *per os* of a sort, may have on the control of gonorrhea. Administration by mouth has disadvantages as well as desiderata, among them especially, the lack of control of doses and assurance that the drug is being taken according to schedule.[25b,c,d,52,64,81] In many particulars intramuscular injection is both theoretically and practically the ideal. No headway has been made in this direction in improving the administration of the trivalent arsenicals in this particular in some time. There is as yet no safe, effective, acceptable intramuscular therapy with the arsphenamines and arsenoxide for adults. Where large bodies of persons must be treated under pressure of time and circumstances, a valuable form of simplification of treatment technique is increased speed. To this Mapharsen[18,35,79] is as important a contribution at the present time as was neoarsphenamine, by the Ravaut concentrated solution technique in the last war.

Precise and unvarying chemical constitution, as demonstrated by crystalline characteristics, which as Tatum[97] points out, does away with the necessity for constant comparative biologic testing of lots, as in the case of the arsphenamines and uniformity of action dependent on uniformity of constitution, are highly desirable qualities in arsenicals for the treatment of syphilis, and are thus far met only by arsenoxide. Several troublesome groups of reactions, including colloidoclastic changes often held responsible for the nitritoid crisis, and possibly allergic sensitization, may perhaps be controlled or done away with by using arsenicals to meet this requirement.

Further reduction of unfavorable reaction-producing effect on the human subject is unquestionably theoretically desirable, but this has a double-edged quality, because reduction in toxicity has so often seemed among the trivalent arsenicals to parallel reduction in efficiency.[5,7b,56] The differentiation of reactions into incommoding *versus* serious, is important for the public health campaign, for incommoding reaction is as serious in discouraging the control of infectiousness by continuity of treatment, and as much opposed to the calendar regularity of schedule now being emphasized, as serious reaction is losing the individual his chance of cure. Every effort should therefore be devoted both to the devising of preparations which retain therapeutic effectiveness despite diminished toxicity, and equal effort should be devoted to such reasonable and practicable refinement of technique as may do away with or reduce the reactivity attributable to the improper or casual handling of a drug. The importance of stability and speed with safety has been repeatedly emphasized by Stokes,[87a] who maintains that hurry, which brings out the intrinsic defects of arsenical drugs other than arsenoxide, is basically responsible for the reaction incidence of clinics and individuals day in and day out.

The gradually increasing recognition of the allergen behavior of the

trivalent arsenicals, as illustrated by sensitization effects in arsenical dermatitis, detection of sensitiveness by patch technique, animal experimental work on the induction and prevention of neoarsphenamine sensitization and so forth, indicates that new preparations should be studied in advance for the incidence and if possible avoidance, of idiosyncratic and allergic effects.[7a,20a,b,26,71,80,93,94] Several of the gravest reactions to the arsenicals, including particularly the so-called hemorrhagic group, have an unpredictability that needs further study along these suggested lines.

The distribution and behavior of the arsenicals in the body still remains a tissue of speculation rather than an orderly array of facts. It may be too much to hope that the "tagged" atom may help us out in this direction; but certainly if the notion is physically entertainable at all, the arsenicals should not be forgotten in the current work based upon the cyclotron. Arsenoxide, particularly because of its crystalline structure, might conceivably be investigated from this standpoint.

Process of Evaluation of Arsenicals. The clinical testing of the arsenicals and thus the determination of the status of new preparations, has long been a weak spot. The tremendous importance of uniformity of performance is at present committed practically entirely to a trypanocidal test which is a useful but essentially foreign laboratory procedure for a spirochetal disease, and to a laborious and extended clinical tryout, the weaknesses of which as well as its value, are demonstrated by such papers as that of Snodgrass,[85] of Kolmer,[49] of Moore, Hardy, Robinson and Eagle,[54] of Harrison,[39a] of Stokes and Beerman[7c,90] and of Cole.[17] The correlation of trypanocidal tests, spirillicidal tests in rabbits, clinical curative effects in rabbits, and the above described complex series of questions governing effect in man, often exhibit serious hitches and disagreements. It deserves repeated emphasis that the behavior of an arsenical in the animal is a guide but not an infallible criterion for its behavior in man. Clinical testing of the relative efficiency of five types of arsenical in the treatment of syphilis were shown not to depend upon a popular method of evaluation—that of the rate of reversal of serologic reactions in early syphilis, by Moore and his coworkers. All five drugs (arsphenamine, neoarsphenamine, silver arsphenamine, Bismarsen, Mapharsen) were shown to reach approximately the same destination in the end with respect to this single criterion.

Cannon and Karelitz[12] demonstrated the difference between three drugs with respect to the time and dosage factors in serologic reversal. Beerman[7d] has even pointed out the possible effect of bismuth in positively delaying serologic reversal, a finding suggested by the curve of Bismarsen reversal obtained by Moore *et al.* Harrison's paper emphasizing the inconstancy and variability of the rate of disappearance of *Spirochæta pallida* from secretions of early syphilitic lesions following administration of equivalent doses of a variety of batches of neoarsphenamine and arsphenamine as well as sulfarsphenamine and solusalvarsan, illustrates not only the importance of clinical testing of drugs for uniformity of spirillicidal action in man, but suggests variation in host[87a] as well as strain of spirochete,[7b] in addition to the apparently quite clear-cut lot differences among the various manufactured brands. Snodgrass[85] in reviewing the points for investigation rates a

test of clinical effect on late syphilis as the next objective after a study of toxicity, a point on which Stokes and Beerman[90] differ with him. The latter maintain that a drug which is not rapidly and effectively spirillicidal in early syphilis should not be released to the medical profession for use in the treatment of syphilis, because of its failure to meet the public health objectives of controlling the spread of the disease. Drugs of slow spirillicidal effect, however, are not useless, inasmuch as they may be of particular value in the treatment of cardiovascular syphilis, in the avoidance of therapeutic paradox, and in the reduction of persistently positive serologic reactions of the blood to negative. Such drugs may also be substituted if ultimately of good effect for reaction-producing spirillicidal drugs employed early in the disease.

Stokes and Beerman discuss, as does Snodgrass, the type of organization, clinical and scientific, which should be charged with the clinical testing of the arsenicals. All these authors emphasize the dangers of the too often commercially exploited general practitioner's report based on a few samples used under uncontrolled clinical and laboratory conditions. The only opinions which should be accepted on the worth of antisyphilitic drugs are those of large well-equipped clinics with competent laboratories working in association with them. In order within such organizations to produce trustworthy work, the clinical investigator must (Stokes and Beerman): 1, subdivide his reports chronologically into periods, and use only identical periods for comparisons, especially of reactions, some of which seem influenced by wave-like "epidemiologic" factors; 2, accept for testing only drugs for which he has the proper clinical material in sufficient amounts; 3, maintain a stable evaluating mechanism, including a laboratory equipped for controlled serologic and darkfield examinations and clinical assistants with not less than 2 years' experience with the disease; 4, have available a follow-up mechanism of not less than 60% efficiency which will secure continuity of treatment, and return for reëxamination over a long period of time; and 5, develop a treatment organization whose performance is constant with reference to the technique of injection, and a normal incidence of unavoidable reaction to ordinary drugs, and which has developed special facility and accuracy in detecting both therapeutic response and reaction to the new drug. It is important to emphasize the time factor in clinical testing which Stokes and Beerman estimate to range from 2 months to 2 decades, depending on the point to be covered.

Laboratory Testing of the Arsenicals. This has until recently been subject to the labor, expense and time consumed by the use of the rabbit and rat as experimental animals, which has virtually necessitated the maintenance of an animal hospital organization in charge of specialists in rabbit syphilis. With the chemical synthetic establishment required the set-up has increased the expense of the manufacture of the arsenicals so that a new drug is almost bogged down by the cost of its introduction before an ampoule is marketed, and the interest of manufacturers is significantly reduced. It is an interesting point in Government regulation of testing and marketing of the arsenical synthetics that the Congressional Act[2] enabling the Public Health Service to control such products is so worded that only drugs like the arsphenamines can be included under the testing of "biologicals." A drug such as

arsenoxide, now of enormous and extending importance, cannot, because of its molecular constancy and crystalline character, be subjected under the present law to any form of governmental regulation.

The relation as evaluating devices between trypanocidal and spirocheticidal tests for the efficiency of an arsenical has been specially studied again by Probey,[65] who points out that the minimal effective dose of neoarsphenamine in experimental syphilis may vary from test to test, probably due to the variable factors in the experimental infection, to which the virulence of the organism may contribute, rather than to differences in the curative value of the drugs. He found 17 lots of neoarsphenamine however, representing 7 American brands, to be uniformly active in curing experimental syphilis in rabbits with one treatment late in the active stage of the disease.

The effort to get away from the "animal" type test procedure has led to Eagle's devising a method[23a,b,c,d,e,f] for the testing of spirocheticidal effect *in vitro*, of which Kolmer and his associates[46,50] offer a critique. Sanyal,[75] incidentally, has pointed out the possible usefulness of an electrolytic toxicity test. Eagle tests the spirocheticidal action of graded strengths of the various antisyphilitic arsenicals in saline solution. His demonstration of their spirillicidal properties *in vitro* sets aside the long-established dictum that the trivalent arsenicals are relatively non-spirillicidal outside the body. In editorial comment[25a] on this method the *American Journal of Syphilis, Gonorrhea and the Venereal Diseases* rates Eagle's *in vitro* test as a major contribution to the control of present, and the study of new, arsenicals. Kolmer, Kast, Peterson and Rule,[46,50] while confirming Eagle's reëstablishment of *in vitro* spirocheticidal effect, point out that dilution, duration of exposure, temperature and other important control factors so modify the usefulness of the test, that many of the interpretations offered to date should be reviewed. The method undoubtedly involves complex control factors. Some interesting paradoxes are emphasized by Kolmer *et al.* Mapharsen, for example, was found to be 2 to 4 times more spirocheticidal and trypanocidal than arsphenamine and neoarsphenamine *in vivo*, but, paradoxically, about 5 times less spirocheticidal *in vitro*. Unquestionably this method will bring about some important revisions in technique and interpretation from the laboratory side in the evaluation of the arsenicals.

New (and Old) Drugs. The Drug-of-the-Year (or half-decade) is arsenoxide, whose revival by Tatum[97] and application to the general therapy of syphilis by his clinical associates, Lorenz and by Foerster[31,101] and also in mass study by Gruhzit and Dixon,[35] is probably the most important single contribution to the arseno-therapy of syphilis since the introduction of neoarsphenamine. The bibliography of arsenoxide (Mapharsen) or as Tatum says, arsenoxide from the arsphenamine, already at this writing includes more than 150 titles. Judged by the short-term elements in the standards of evaluation previously mentioned, arsenoxide (Mapharsen) has met every requirement. It is rapidly spirillicidal, and convincingly effective in the healing of lesions, reduction of serologic tests to negative, and other forms of symptomatic response. For the length of time it has been in use it has an excellent record in the prevention and control of asymptomatic neurosyphilis. The bibliography of the drug is as yet deficient in thoroughgoing study

of infectious relapse. In late syphilis of special systems it is at least as effective as the arsphenamines; in late syphilis of the nervous system, no more and no less effective. Its worth in pregnancy is probably, though not as yet demonstrably, that of the arsphenamines, though Castallo, Coppolino, Rakoff, Roeder and Dickson[13] in a group of 116 pregnant women, treated with Mapharsen and bismuth, rated the drug definitely less effective than neoarsphenamine in the treatment of syphilis in pregnancy, because it does not afford as good protection to the fetus during the period of treatment and complications in the mother, especially gastro-intestinal, are more frequent than they should be. Morgan,[55] treating congenital syphilis, rates it more effective in reversing serologic tests than any other arsenical compound previously used. Cornell and Astrachan[21] gave the drug intramuscularly, and refused to draw conclusions as to its effectiveness on account of the low dosage employed. Howles[41] found this drug good in his experience in treating 204 congenital syphilitics. Chargin and Leifer[15] treated 50 consecutive Wassermann-fast patients with Mapharsen, to find that the drug is neither more nor less effective than any other arsenical in the management of this type of patient. Cole and Palmer,[18] in a careful study of 242 patients, of whom 185 were in the primary or active secondary stage, employing a total of more than 5000 injections, apparently rate the drug as approximately the equal of the more familiar arsphenamines. There is a notable absence in the literature of comparative series run in similar conditions in the same clinics, using Mapharsen parallel with the older arsenicals.

One of the strongest "talking points" for Mapharsen is the undoubtedly greatly reduced incidence of reaction to this drug. Nitritoid crises, often a serious annoyance with the older arsenicals, is all but absent with Mapharsen. Epstein,[26] compiling data from 92,000 Mapharsen injections, found skin reactions, including exfoliative dermatitis, from one-half to one-third or even one-ninth as frequent as with the standard arsenicals. This is especially true of exfoliative dermatitis. Rein and Wise[69] listed 19 types of reaction recorded to 1939, including practically everything made familiar by the older arsenicals except aplastic anemia, of which at the time of their writing there was not a single recorded case. They report 1 death, but fatal accidents are certainly extremely few.[48,67,82] One of the strongest tributes to the low toxicity of arsenoxide is the experience of Baehr-Chargin group,[3] working with the intravenous drip technique, in which the substitution of Mapharsen in total dosage as high as 1200 mg. has not served to approach the toxicity of neoarsphenamine in an average dosage of 4 gm. (4000 mg.). On the staying power of Mapharsen very little is as yet of necessity available. Raiziss and Severac[66b] found the toxic and curative dose so close to each other in animal studies that they felt arsenoxide was under a grave handicap. Colonel Harrison (personal communication) has expressed the opinion that the most serious deficiency of Mapharsen will be in the direction of permanence of results. Taking into consideration all the various factors entering into the efficiency of an arsenical, it seems reasonable to expect that as in the case of neoarsphenamine, any existing intrinsic deficiencies will be taken up in the modern systems of treatment by the use of bismuth as a heavy metal,[39b,88,89,91,96] bringing the level of effectiveness of com-

bined Mapharsen-bismuth therapy fully up to the standards achieved by the conventional arsphenamine and neoarsphenamine therapy by combined continuous (CCG) therapeutic systems.

Always more or less parenthetically, but nonetheless usefully, it should be pointed out that Mapharsen is a valuable substitute for other arsenicals, when these have proved reaction-producing in the individual case. Reports on this matter include those of Jordon and Traenkle,[45] Goldberg,[33] Schoch,[80] Epstein and Falconer,[28] Falconer and Epstein.[29]

Acetyl-glycarseno-benzene (Solu-salvarsan),[30,70,74,76–78,100] manufactured in Germany, was submitted to the therapeutic trials committee of the British Medical Research Council in 1933, and reported on by Colonel Harrison in 1939.[39c] In 1940, Guy, Goldmann, Gannon and Slone[37] published an American report of the preparation. This drug has intrinsic theoretical interest because it has apparently no sensitizing properties for animals as distinguished from other arsphenamines, and might therefore conceivably be expected to give rise to fewer idiosyncratic or allergic reactions in man. A concise clinical summary of the two mentioned reports is furnished by the Council on Pharmacy and Chemistry of the American Medical Association.[1b] Colonel Harrison and his coworkers found that the drug was not as effective as neoarsphenamine; its spirillicidal period in early lesions being as long as 6 days. Instead of being painless, as was hoped, on intramuscular injection, pain was quite frequent, and reactions far from rare, many of them severe, and even fatal. The American authors[37] likewise found the reaction incidence to be too high to recommend the drug. Sensitization dermatitides which it was hoped would not develop, and blood dyscrasias likewise appeared in the American series. The drug was therefore given only preliminary status, and not recommended by the Council on Pharmacy and Chemistry.

Thio-arsene (disodium bis-(p-sulfophenyl)(acetamido phenyl)-dithioarsenite), a solution of the mono-ethanolamine salt of sodium p-thiophenyl sulfonate, is added in preparation. Experimental animal results seem to justify its trial in man; Robinson and Moore,[72] from the Johns Hopkins Hospital, however, report so high an incidence of severe gastro-intestinal reaction as to necessitate marked reduction in the advised dose. The reactions are so severe, that patients refuse to continue treatment with the drug. It cannot be used in patients who have had a dermatitis from the previous use of the arsphenamines. It compares unfavorably with the arsphenamines, and with bismuth in its effect on surface spirochetes, on the healing of lesions, and on the blood Wassermann reaction. Becker and Obermayer[4] reported on the use of the drug simultaneously with bismuth but since the series was uncontrolled by a group treated by bismuth alone, conclusions are unsatisfactory. The drug should therefore not be recommended for use at the present time.[19,24]

Trisodarsen (trisodium salt of 3,3′ diamino 4,4′ dihydroxyarsenobenzene N,N′ dimethylene sulfonic acid) has had quite an extended and carefully conducted clinical trial at the hands of the Syphilis Clinic of the University of Pennsylvania and of Givan and Villa[32] in the Pediatrics Department of the Long Island College of Medicine, and the Brooklyn Eye and Ear Hospital. The former authors found the reac-

tion incidence compared with several other series, including arsphenamine, neoarsphenamine and Mapharsen, to compare favorably with and even to be lower with respect to mild reactions than that of most of the named drugs. With respect to severe reactions, there was some tendency to increased frequency of dermatitis and hemorrhagic reaction, as previously observed in most of the sulfarsphenamine group of drugs. The distinctive characteristics of Trisodarsen include superiority to neoarsphenamine with regard to the rate of healing of primary and secondary lesions; and effect on the serologic reactions of the blood, intermediate between neoarsphenamine and arsphenamine; an exceptionally low incidence of asymptomatic neurosyphilis as evidenced by spinal fluid examination. In subsequent investigations covering a period of 8 years, this position has been reasonably well maintained. It would appear that the superior clinical effectiveness of the drug must be measured against an undoubted tendency to dermatitic and hemorrhagic reaction, which is relatively rare with Mapharsen for example. Givan and Villa, employing Trisodarsen in congenital syphilis, reported it well tolerated by the intravenous and intramuscular routes, and particularly free from paravenous infiltration when the drug was delivered outside of a vein. Gastro-intestinal reactions are more numerous than the average, but are attributed by these observers to fright on the part of the children. The drug can be substituted in patients having reactions to neoarsphenamine. It was markedly effective in the treatment of interstitial keratitis, and an unusually high reversal of positive Wassermann reaction (76%) was secured by the use of the drug alone or in combination with other drugs. The tonic effect was notable.

Bismarsen (bismuth arsphenamine sulfonate), on the market 14 years, has been reported since 1931 by many authors.[6,14,36,38,51,57,66a,68,90,92,95,98] The substance of these evaluations is that Bismarsen has an established field of usefulness, and is at its best in the treatment of children and in cardiovascular syphilis. It cannot be given intravenously, but is of material usefulness where the intramuscular route is the only one available. The long series of relatively frequent injections (twice weekly) necessary to the best results in early syphilis are a handicap to its use in this phase of the disease, and it has demonstrated no superiorities in the treatment of latent and late syphilis other than cardiovascular. The reaction incidence is low, but as in the case of Trisodarsen, exhibits a tendency towards hematopoietic accidents, which seem to accompany the sulfarsphenamine group of drugs. Such reactions are, however, rare.

Sulfarsphenamine exhibits the curious paradox of warm allegiance on the part of some undoubtedly competent observers, side by side with damnation from others equally competent. This drug relatively non-reaction-producing and therapeutically effective when given to children, has been subjected to so much criticism on the score of grave reaction produced in adults (hemorrhagic and hematopoietic injury and dermatitis) that its status was reviewed by the Council on Pharmacy and Chemistry in 1932[1a] and the *pros* and *cons* there discussed. The late Dr. Albert Pfeiffer[62] who strongly supported its continued general use by the New York State Department of Health compared the reaction incidence in 29,510 reactions with the statistics of the Coöperative

Clinical Group, insisting that sulfarsphenamine's record was fully equal to that of the other arsphenamines. He stated that in the New York State Clinics, there were no cases of aplastic anemia, cerebral hemorrhage, acute yellow atrophy or ocular damage, and no deaths from the drug. Osborne, Rickloff and Butler[58] in parallel tables showed that the incidence of jaundice was 1 in 800 injections for arsphenamine (606); for sulfarsphenamine 1 in 179 injections. Dermatitis occurred in 1 of 859 injections following arsphenamine, whereas it occurred in 1 of 298 injections following sulfarsphenamine. There were no cases of purpura following arsphenamine, whereas 2 followed sulfarsphenamine. The United States Navy Medical Department,[86] using sulfarsphenamine from 1925 to 1939, among 29,438 injections, reported 17 mild, 8 severe and no fatal reactions to sulfarsphenamine. During the year 1939, 943 doses of this drug were administered with no reactions whatsoever. In the 15-year period the incidence of reactions of 1 to 1178 doses of sulfarsphenamine is somewhat higher than the average ratio of 1 to 1470 doses of 8 arsenicals, trivalent and pentavalent. In general, it is clear therefore that the weight of opinion is opposed to the use of this drug in adults, but sanctions its use in the treatment of children.

Silver arsphenamine continues to be used with accumulating evidence that it is really from the therapeutic standpoint one of the most effective of the arsphenamines. Cannon,[11a] in comparing it with arsphenamine and neoarsphenamine, found serologic tests reversed in a fewer number of injections of silver arsphenamine, a smaller amount of the drug, and a slightly shorter length of time than the neoarsphenamine. Its superiority over neoarsphenamine was apparent also in the healing of lesions, and in the achieving of "satisfactory" end-results it stood only very slightly below neoarsphenamine. The fear of argyria which has had an important influence on the use of this drug is well grounded. Pillsbury and Hill[63] collected 19 cases of argyria from the use of silver arsphenamine. In their summary it stands third among all silver compounds responsible for argyria. While this incidence is not intrinsically high in proportion to the use of the drug, the complications are so disconcerting and medicolegally serious as materially to discourage the use of the drug.

The comparative values of arsphenamine (606) and neoarsphenamine (914) have been so many times reviewed that only a brief summary seems necessary. All syphilologists of experience concede to "AB" (arsphenamine 606) the premier place among all arsenicals for the treatment of syphilis (other than paresis). Cannon[11b] who has especially carefully studied this question and consistently maintained the superiority of 606, and who has devised a syringe technique for its use, seems to have established the position of the drug beyond peradventure. There is much evidence that the toxicity of 606 is steadily on the decrease, probably due to improved methods of manufacture, and that it is now probably the least toxic of all the arsphenamines. Whether Cannon's[11c] simplified technique which employs large syringes, can achieve enough popularity to reintroduce the drug to practice, remains to be seen. Neoarsphenamine is now the most reaction-producing of the standard and generally accepted arsenicals in the treatment of syphilis. Its therapeutic worth has been reënforced by bismuth so that the modern systems in which it is employed are as effective as

those employing 606. Whether or not Mapharsen with its lower reaction incidence and quicker and simpler administration can displace it altogether from practice should, and perhaps will, depend on the demonstration for arsenoxide, of an equal ultimate effectiveness in cure. No changes have been made in the physical and chemical characteristics of marketed neoarsphenamine which justify any change in the established technical features of its administration, namely, no agitation or aëration on mixing, and extremely slow injection. Apparently the work of Probey[65] indicates that much of the lack of uniformity and therapeutic efficiency of various lots of neoarsphenamine among American manufacturers at least has been ironed out.

New Techniques in the Use of the Arsenicals. The previous discussion has indicated that neoarsphenamine has now an established place in the standard therapeutic system for the treatment of syphilis, including those of the United States Public Health Service and Coöperative Clinical Group ("30-60-03" and "24-60-100 plus"),[87b] and in the British-Scandinavian intermittent system published parallel with the American Continuous in the League of Nations Special Commission report. There is therefore no longer anything to be gained by the criticism of the practitioner who uses neoarsphenamine as the easier of the two available drugs for, as has been indicated, bismuth has apparently taken up the shortcomings of the weaker arsenical, and produced an ultimate result essentially equal to that attained by the use of 606. Attention should be directed therefore to other matters, such as the disappearance of the differential in dosage between male and female, both being treated essentially alike; the optimum arsphenamine and neoarsphenamine dosage based on weight; the superiority in ultimate results of large over small doses; and the tendency to use longer series of injections with neoarsphenamine and Mapharsen than with 606. The continuity of treatment during the arsenical phase in the treatment of early syphilis is repeatedly emphasized by all American studies as demonstrably superior to any form of intermittence practised in this country. As yet no satisfactory studies have been made of the reason for the conspicuous rapidity of reversal of serologic tests which occurs in early syphilis under the arsenical alone, particularly in the case of 606, and the lag which follows the employment of a heavy metal, especially bismuth. That there is a considerable range of intensity possible in what has ultimately been shown to be effective treatment of syphilis with the arsenicals is apparent from Padget's[61] recently published study of the treatment of early syphilis and from the description of the intensive system of treating the transient syphilitic at the United States Public Health Service center at Hot Springs, Arkansas. As described by Waugh and Milovich[99] in a discussion of severe reactions to arsphenamine, the "doubled-up" initial course compares with the old Southard and Solomon system for the treatment of paresis minus the doubling of the standard dose. The incidence of severe reactions under such a régime is somewhat higher than under the generally accepted figures of the Coöperative Clinical Group, for a less intensive type of treatment (2.44 severe reactions per 1000 arsenical injections, as compared with 1.99). The increase in frequency of reaction, however, can hardly be described as proportionate to the increase in intensity. At the Hot Springs Clinic the incidence of icterus was 84% higher

and crustaceous dermatitis 10% lower under the intensive system than under the standard relatively milder systems of the Coöperative Clinical Group.

Intensification has, of course, reached its peak in the universally interest arousing so-called 5-day treatment system for early syphilis which has been continuously studied by the Baehr-Chargin group[3] in New York. It is, of course, impossible to offer a final evaluation of such a technique at this stage of its use. The unfortunate consequence of a premature popular excitement and demand has been visited upon this system of treatment, notwithstanding reasonable caution in reporting it to the medical public. The original publications by Hyman, Chargin and their associates[16,40,42a,b,43] was followed by another report by Hyman, Chargin and Leifer in 1939,[44] which led apparently to the placing of the investigation in the hands of a committee headed by the Surgeon-General of the United States Public Health Service and the Commissioner of Health of New York City. The report of the members of this committee at a conference called by the Commissioner of Health on April 12, 1940, is a succinct, carefully prepared and excellently controlled statement of technique, complications, reactions, and clinical results to date. In the discussion of the method which followed, general recognition was given to the importance of the drip or continuous method of administering a parasiticidal drug as a significant clinical advance. It was indicated, however, by the discussion that the work conducted to date was insufficiently supported by laboratory studies on animals, particularly with reference to toxicologic effect. It was clear that the reactions induced by the treatment chiefly preoccupied the commentators, and Moore in discussion was particularly vigorous in directing attention to the high incidence of hemorrhagic encephalitis whose frequency, 1 to 100 in the 5-day series, compared very unfavorably with perhaps an incidence of 1 to 15,000 under the standard treatment systems. Generally speaking, the reports failed to demonstrate within the limitations of time and observation any striking superiority in aggregate cures and absence of relapse over the standard systems of longer duration such as those of the Coöperative Clinical Group. The materially greater safety of Mapharsen employed in the 5-day system's second series and the possibility of developing modifications of the system in the form of repeated injections during each 24-hour period without the necessity for continuous intravenous drip have also received attention. It is generally agreed that the method is one for specialists under the most rigidly controlled conditions, and is not to be commended in the present state of knowledge to the practising physician or for general use. So far as can be judged from the available publications, the chief merit of the method is that of time-saving rather than safety or superiority of ultimate results. Whether or not time-saving in itself justifies the greater assumption of risk, or is even a desideratum in and of itself, is a proper matter for future evaluation.

The report of the Council on Pharmacy and Chemistry in the *Journal of the American Medical Association* in 1940[25e,f] seems generally to be in accord with this estimate.

Non-specific Uses of the Arsenicals and Combinations of Their Use With Non-specific Measures. It is too easily forgotten in the emphasis on arsenicals as specifics, that a considerable portion of their effect is

probably not directly upon the *Spirochæta pallida* and that they are significantly useful in other conditions than syphilis. The outstanding evidence of this, of course, is the action of tryparsamide, a practically non-spirillicidal pentavalent arsenical, upon a highly specific manifestation of neurosyphilis, namely, general paresis. Several recent publications deal with the non-specific effects of the arsenicals in conditions other than syphilis. Duehr, Weissmiller, McIntosh, Cooper and Tatum[22] have directed attention to arsenoxide (Mapharsen) as a therapeutic agent for *Vincent's infection*. Apparently it is at least as effective as neoarsphenamine when used locally and the authors claim for it quicker and more satisfactory results than those obtained by any other agents. The technique, as illustrated by 1 of their cases, consists in the use of Mapharsen mouthwashes or a swab of a 1% solution of the drug with a gargle of 0.4% of the drug and the intravenous injection of 30 mg. of Mapharsen for the initial dose and three successive intravenous injections of 60 mg. each at 4-day intervals. An alkaline gargle is recommended to clear the mucosæ of secretions before the Mapharsen mouthwash is employed. Young and McLendon[102] report on the treatment of *induced malaria* in negro paretics with Mapharsen and tryparsamide. It has apparently been claimed that quartan malaria responds in these patients as satisfactorily to Mapharsen and bismuth as to quinine. Goldman[34] is quoted even as rating Mapharsen as immeasurably more effective than quinine in quartan infections, and notably more effective than arsphenamine and neoarsphenamine. He employed arsenoxide for the termination of tertian malaria in place of quinine. Young and McLendon[102] took pains to control their use of arsenoxide and tryparsamide for the termination of quartan malaria by reëxamination of blood smears as long as 22 weeks after the completion of the Mapharsen course, and found all of their patients to have become asymptomatic malarial carriers. Three of their quartan malaria patients who received tryparsamide examined 1 year after the completion of tryparsamide treatment still showed *P. malariæ* in the blood stream. The use of the arsenicals for the purpose of terminating malaria unaided by quinine would therefore seem unwise.

Rosebury, Foley and Rights[73] report on the effect of neoarsphenamine and sulfarsphenamine in *experimental fusospirochetal infection* in guinea-pigs with almost uniformly disappointing results. Both neoarsphenamine and sulfarsphenamine were ineffective when administered systemically and only ameliorative when administered intralocularly into the center of the lesion. Of the two neoarsphenamine was the more effective. Osgood, Brownlee and Joski[59,60] studied the relative effectiveness of neoarsphenamine, Mapharsen, sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethylthiazole on infections with *Strep. viridans* in bone marrow cultures. Neoarsphenamine in concentrations of 1 to 150,000 was effective against more strains than any of the other drugs tested, but was less effective than sulfathiazole or sulfapyridine against certain strains. In a concentration of 1 to 1,500,000 it is effective against certain strains, but not as uniformly effective as neoarsphenamine in concentrations of 1 to 150,000.

Buchtel and Cook,[10] from the Mayo Clinic, employed neoarsphenamine in treatment of *infections of the urinary tract* in a total of 250 cases, with marked success, in pyelonephritis of coccal origin but not in bacil-

lary pyelonephritis. The drug fails in the presence of stones, marked obstructions, severe focal infection, infection referable to *Strep. fecalis*, non-specific prostatitis, and chronic cicatricial pyelonephritis. Acidification of the urine improves the result. Small doses, interestingly enough, are as efficacious as the larger ones, and improvement will occur after the first or second injection, if it occurs at all.

The use of the *arsenicals in conjunction with fever therapy* is probably more general and developing more rapidly than the available literature indicates. Simpson was among the earlier enthusiasts in recommending the simultaneous use of antisyphilitic drugs (Bismarsen or neoarsphenamine and bismuth) and fever therapy in early syphilis.[83,84] Kemp[47] pioneered in the simultaneous use of tryparsamide and hyperpyrexia in the treatment of paresis. Epstein[27] reported a series of 87 patients with central nervous system syphilis who were treated with fever therapy produced by the blanket method and with drug therapy consisting of tryparsamide and bismuth salicylate, or occasionally, neoarsphenamine simultaneously. This combined use of chemotherapy and artificial fever therapy gave excellent results. Bennett and Lewis[8,9] reported on 72 cases of asymptomatic and clinical neurosyphilis treated by combined artificial fever and chemotherapy. Of 10 of their cases strongly positive cerebrospinal fluid findings were reported as completely reversed to negative in 7, and partially reversed in 2, by the combination. In 19 patients with paralytic dementia, treated by the combined method, complete remission with full occupational recovery followed in 14, moderate improvement in 3, and no improvement in 2. In 31 cases of tabes dorsalis of the most severe type, complete relief of all predominating symptoms occurred in 52%, improvement in 35%, and only 4 failed of improvement. Gastric crisis was completely or partially relieved in 11 out of 15 cases. In severe disabling types of meningovascular neurosyphilis, 10 obtained complete relief of predominating symptoms out of 12 treated. Fever was induced by the Kettering hypertherm and Mapharsen or Bismarsen employed as the arsenical. Menagh[53] employed in 130 patients neoarsphenamine in 0.6-gm. to 0.9-gm. doses, beginning with the second bout of fever, and administered in 41 cases with the patient's temperature at 105° F. The drug was well tolerated, and Menagh believes therapeutic efficiency was markedly increased.

It is proposed to prepare a more extended discussion of reactions to the arsenicals as the next contribution to this review.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 18, 1941

The Collection and Analysis of Fluid From Single Glomeruli and Tubules of the Mammalian Kidney. A. M. Walker, Jean Oliver and P. A. Bott (Department of Pharmacology, University of Pennsylvania, and Department of Pathology, Long Island College of Medicine). In anesthetized rats, guinea pigs and opossums a technique has been developed for rendering the kidney accessible to direct puncture of its nephrons in a manner similar to that which was found serviceable in studies of the amphibian kidney. At a preliminary operation a unilateral nephrectomy was performed to allow compensatory hypertrophy of the remaining kidney to occur. The surface of this remaining (left) kidney was protected from exposure by a layer of warm oil and illuminated by light transmitted through a lucite rod. Punctures of tubules and, in a few cases, of glomeruli was accomplished by quartz pipettes and fluid was collected in amounts sufficient for ultramicroanalysis (0.1 to 1 c.mm.). After marking the punctured nephron by the injection of ink for subsequent identification, the kidney was fixed in formalin, macerated, and the nephron isolated by microdissection in its entirety. By means of stereoscopic photographs and camera lucida

drawings, accurate measurement of the various segments were then made which exactly identified the site of puncture.

Sixty successful experiments have been performed. The results show that gomerular fluid is free from detectible amounts of protein, has the same vapor pressure as blood plasma and contains reducing substances and exogenous creatinine in the same concentration as occur in plasma water. Glucose is reabsorbed by the proximal tubule in these animals as in amphibia. The increasing concentrations of creatinine and glucose (after phlorhizin) in tubule fluid indicate that the proximal segment reabsorbs about 80% of the fluid in glomerular filtrate; this fluid reabsorption is accomplished without any increase in vapor pressure of the tubule contents. The tubule fluid plasma concentration ratio of chloride reaches 1.5 early in the proximal tubule; this finding, in view of the vapor pressure observations and of preliminary sodium analyses, implies the preferential reabsorption of another anion ($-HCO_3$?) by the proximal segment.

Correlation Between the Secretory Power of the Frog Kidney and the Molecular Configuration of Organic Compounds. Rudolf Höber (Department of Physiology, School of Medicine, University of Pennsylvania). In previous experiments on the isolated Ringer perfused frog kidney, it has been found that the sulphonic acid azo dyestuffs undergo secretory transfer across the proximal tubules, provided the sulphonate groups are attached to one of the molecular halves of these dyes, whereas the distribution of the sulphonate groups to both halves, in general, impedes the secretion. It was concluded that a polar-non-polar or a hydrophilic-organophilic structure is a prerequisite for the attachment of the dye molecule to the surface of the kidney cells. These previous studies have been extended with the use of more simple organic compounds. The kidney was supplied with only one-half of the azo dye molecules and this half, upon reappearing in the secretion, was coupled in a diazo reaction to the other half and determined colorimetrically. The following results were obtained: the monosulphonates of naphthylamine, naphthol and aminonaphthol, irrespective of the mutual location of the NH_2, OH and HSO_3 groups, appear in the secretion at a higher concentration level than that in the perfusion fluid, whereas the disulphonates fail to become accumulated. It is suggestive to interpret these results in a way similar to that proposed with regard to the behavior of the azo dyestuffs: organotropic affinities are exhibited by the naphthalene ring system as well as by the NH_2 and OH groups, hydrotropic affinities are exhibited by the sulphonates. If the opposing forces balance each other, there is an attachment of the molecule at the interfacial boundary, a preliminary step in the active transfer. This hypothesis is supported, for instance, by comparing: 1, aminonaphthalenesulphonic acid; 2, sulphanilic acid; 3, sulphanilyl-sulphanilic acid; 4, sulphanilyl-sulphanilamide; 1 and 3 were concentrated in the secretion, 2 and 4 were not.

Application of the Heart Rate Recorder to Pharmacological Research. Klaus Unna and Michael Kniazuk (Merck Institute for Therapeutic Research). A method has been demonstrated which permits the continuous recording of the heart rate on an ordinary smoked paper kymo-

graph simultaneously with other recordings in experiments on anesthetized animals. The method is based on amplifying the heart potentials and feeding the amplified impulses to a mechanical counter. The heart potentials are picked up by electrodes from the mouth and the rectum of the animal and amplified by a portable A.C. operated amplifier. The amplified impulses are counted by a mechanical counter which consists of two electromagnetic step motors that alternate automatically, each counting for a period of 10 seconds. The total number of impulses received during this interval is recorded on the kymograph by a writing point connected to the counter by a cable. The number of impulses is recorded as a proportional linear displacement. A difference of one impulse per 10 seconds is clearly visible. The counter is adapted to record frequencies up to 400 per minute.

Experiments have been presented demonstrating the effect of adrenalin, atropine, carbamylcholine and digitoxine on the heart rate as measured and recorded by this method.

Isolation and Properties of a Pigmented Complex Macromolecular Material From Streptococcus Pyogenes. M. G. Sevag, J. Smolens, and Kurt G. Stern (Department of Bacteriology, University of Pennsylvania, School of Medicine, and the Laboratories of Physiological Chemistry, Yale University, School of Medicine). A pigmented complex macromolecular material has been isolated by ultracentrifugal methods from *Strep. pyogenes* disintegrated by sonic vibration. The size and complexity of this substance are comparable to some of the viruses isolated from animal sources. This material, in solution, is dark green, opalescent in reflected light and clear in transmitted light. Its chemical analysis is: 9% to 10% total nitrogen, 0.8% to 1% phosphorus, 0.75% to 0.82% purine nitrogen, and 10% to 17.2% lipid. The presence of purine nitrogen, phosphorus, and the positive orcinol test show that it contains nucleoprotein. The nucleic acid has been characterized as a d-ribose type. Serologic data show that this material also contains a group-specific carbohydrate. In addition to these constituents a green pigment is present. The pigment has not as yet been characterized. Tests for Fe, Mg, Ni, and Cu are negative. The density of the macromolecular substance is 1.22, and its specific partial volume 0.816. By means of the analytical ultracentrifuge the sedimentation constants are found to range from 110 —to 548 $\times$ 10^{-13} cm/sec/dyne for 8 determinations. The average calculated diameter is 42 millimicrons. The method of preparation and the presence of molecules of varying but overlapping sizes appear to be responsible for the variation of the sedimentation constant.

Measurement of Sensitivity of the Smallest Blood Vessels in Human Skin to Graded Mechanical Stimulation. S. R. M. Reynolds (Department of Physiology, Long Island College of Medicine). The immediate object of this study was to devise a simple procedure by which it would be possible to measure the sensitivity of the smallest blood-vessels in human skin. This was desired in order that comparison might be made of the sensitivity of the blood-vessels in different individuals and in the same individual from time to time. No present method appeared to do this. Of the known physiologic responses of

the smallest vessels, those to mechanical stimulation seemed to lend themselves most suitably to the purpose. It is well known that a light but adequate stroke will elicit a transient area of paleness of the skin resulting from constriction of the capillaries; that a heavier stroke will give rise to a strong, continuous red line of vasodilatation against a surrounding background of constriction. A device was constructed whereby it was possible so to regulate the force (weight) applied and the speed of its application over a given region (from which duration of the stimulus was determined) that a response intermediate between those described above could be obtained. This threshold response consists of an area of vasoconstriction in the center of which is a just, but easily discernible beginning red reaction. It is possible to read the reaction to within less than $\pm 10\%$ of the weight applied. It is found that a typical strength-duration curve is obtainable; that it represents threshold responses throughout; that it is quite constant, from day to day, for a given individual. The effects of certain experimental procedures were determined. These include the effects of complete circulatory stasis, partial venous occlusion, systemic anoxemia and hypercapnea, and elevation of the skin temperature. Following the suggestion of Lassalle, an index of the excitability for the several curves was determined. By the use of this, the relative sensitivities of the blood-vessels of different individuals is made. A normal average value from which statistically significant values may be appraised remains to be determined. When this is done, it should be possible to study sex, age, seasonal, climatic, pharmacologic, pathologic and other influences upon the sensitivity of the smallest blood-vessels of the human skin.

ERRATUM.

In the article by Reinhold, Flippin, Schwartz, and Domm in the January 1941 issue a comma should be added after "100 cc." on page 107, line 3, so as to read: "Because of the low solubility of the drug in water, about 10 mg. per 100 cc., solutions for standards were prepared by addition of approximately 0.4 cc. of normal sodium hydroxide solution to 100 mg. of sulfapyrimidine crystals."

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